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ATTORNEY'S DOCKET NUMBER
19962YP
U.S. APPLICATION NO. (if known, see 37 CFR 1.5)
09/445054

**TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371**

INTERNATIONAL APPLICATION NO. PCT/US98/08646	INTERNATIONAL FILING DATE 04 June 1998	PRIORITY DATE CLAIMED 05 June 1997
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TITLE OF INVENTION
A METHOD OF TREATING CANCER

APPLICANT(S) FOR DO/EO/US
Neal Rosen, Laura Sepp-Lorenzino, Mark M. Moasser, Allen I. Oliff, Jackson B. Gibbs, Nancy Kohl, Samuel L. Graham and George C. Prendergast

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☐ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(l).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
 - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ has been transmitted by the International Bureau.
 - c. ☒ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
 - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ have been transmitted by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). (UNSIGNED)
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 16 below concern other document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☐ A FIRST preliminary amendment.
☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☐ Other items or information:

EXPRESS MAIL CERTIFICATE
DATE OF DEPOSIT December 1, 1999
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19962YP

17. ☒ The following fees are submitted:

Basic National Fee (37 CFR 1.492(a)(1)-(5)):

Search Report has been prepared by the EPO or JPO.....\$840.00

International preliminary examination fee paid to USPTO

(37 CFR 1.482).....\$670.00

No international preliminary examination fee paid to USPTO (37 CFR 1.482)

but international search fee paid to USPTO (37 CFR 1.445(a)(2)).....\$760.00

Neither international preliminary examination fee (37 CFR 1.482) nor

international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....\$970.00

International preliminary examination fee paid to USPTO (37 CFR 1.482)

and all claims satisfied provisions of PCT Article 33(2)-(4).....\$ 96.00

ENTER APPROPRIATE BASIC FEE AMOUNT =

CALCULATIONS

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Surcharge of \$130.00 for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).

\$0.00

Claims

Number Filed

Number Extra

Rate

Total Claims

32

-20=

12

X \$18.00

\$216.00

Independent Claims

4

-3=

1

X \$78.00

\$78.00

Multiple dependent claim(s) (if applicable)

+ \$260.00

\$0.00

TOTAL OF ABOVE CALCULATIONS =

\$390.00

Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).

SUBTOTAL =

\$390.00

Processing fee of \$130.00 for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).

\$0.00

TOTAL NATIONAL FEE =

\$390.00

Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property +

TOTAL FEES ENCLOSED =

\$390.00

Amount to be

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- a. ☐ A check in the amount of \$0.00 to cover the above fees is enclosed.
- b. ☒ Please charge my Deposit Account No. 13-2755 in the amount of \$390.00 to cover the above fees. A duplicate copy of this sheet is enclosed.
- c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to the Deposit Account No. 13-2755. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Patent Department, RY60-30

MERCK & CO., INC.

P.O. Box 2000

126 East Lincoln Avenue

Rahway, New Jersey 07065

DATE: November 30, 1999

PHONE #: (732) 594-3903

SIGNATURE

DAVID A. MUTHARD

NAME

35,297

REGISTRATION NUMBER

TITLE OF THE INVENTION
A METHOD OF TREATING CANCER

BACKGROUND OF THE INVENTION

- 5 The present invention relates to methods of treating cancer using a combination of an antineoplastic agent and a compound which is an inhibitor of a prenyl-protein transferase.

- Chemotherapy, the systematic administration of antineoplastic agents that travel throughout the body via the blood
10 circulatory system, along with and often in conjunction with surgery and radiation treatment, has for years been widely utilized in the treatment of a wide variety of cancers. Unfortunately, the available chemotherapeutic drugs often fail patients because they kill many healthy cells and thus bring on serious side effects that limit the doses
15 physicians can administer.

- Prenylation of proteins by intermediates of the isoprenoid biosynthetic pathway represents a class of post-translational modification (Glomset, J. A., Gelb, M. H., and Farnsworth, C. C. (1990). Trends Biochem. Sci. 15, 139-142; Maltese, W. A. (1990).
20 FASEB J. 4, 3319-3328). This modification typically is required for the membrane localization and function of these proteins. Prenylated proteins share characteristic C-terminal sequences including CaaX (C, Cys; a, usually aliphatic amino acid; X, another amino acid), XXCC, or XCXC. Three post-translational processing steps have been described
25 for proteins having a C-terminal CaaX sequence: addition of either a 15 carbon (farnesyl) or 20 carbon (geranylgeranyl) isoprenoid to the Cys residue, proteolytic cleavage of the last 3 amino acids, and methylation of the new C-terminal carboxylate (Cox, A. D. and Der, C. J. (1992a).
 Critical Rev. Oncogenesis 3:365-400; Newman, C. M. H. and Magee, A. I. (1993). *Biochim. Biophys. Acta* 1155:79-96). Some proteins
30 may also have a fourth modification: palmitoylation of one or two Cys residues N-terminal to the farnesylated Cys. While some mammalian cell proteins terminating in XCXC are carboxymethylated, it is not clear whether carboxy methylation follows prenylation of proteins terminat-

ing with a XXCC motif (Clarke, S. (1992). *Annu. Rev. Biochem.* 61, 355-386). For all of the prenylated proteins, addition of the isoprenoid is the first step and is required for the subsequent steps (Cox, A. D. and Der, C. J. (1992a). *Critical Rev. Oncogenesis* 3:365-400; Cox, A. D. and Der, C. J. (1992b) *Current Opinion Cell Biol.* 4:1008-1016).

- Three enzymes have been described that catalyze protein prenylation: farnesyl-protein transferase (FPTase), geranylgeranyl-protein transferase type I (GGPTase-I), and geranylgeranyl-protein transferase type-II (GGPTase-II, also called Rab GGPTase). These enzymes are found in both yeast and mammalian cells (Clarke, 1992; Schafer, W. R. and Rine, J. (1992) *Annu. Rev. Genet.* 30:209-237). Each of these enzymes selectively uses farnesyl diphosphate (FPP) or geranyl-geranyl diphosphate as the isoprenoid donor and selectively recognizes the protein substrate. FPTase farnesylates CaaX-containing proteins that end with Ser, Met, Cys, Gln or Ala. For FPTase, CaaX tetrapeptides comprise the minimum region required for interaction of the protein substrate with the enzyme. The enzymological characterization of these three enzymes has demonstrated that it is possible to selectively inhibit one with little inhibitory effect on the others (Moores, S. L., Schaber, M. D., Mosser, S. D., Rands, E., O'Hara, M. B., Garsky, V. M., Marshall, M. S., Pompliano, D. L., and Gibbs, J. B., *J. Biol. Chem.*, 266:17438 (1991), U.S. Pat. No. 5,470,832).

- The prenylation reactions have been shown genetically to be essential for the function of a variety of proteins (Clarke, 1992; Cox and Der, 1992a; Gibbs, J. B. (1991). *Cell* 65: 1-4; Newman and Magee, 1993; Schafer and Rine, 1992). This requirement often is demonstrated by mutating the CaaX Cys acceptors so that the proteins can no longer be prenylated. The resulting proteins are devoid of their central biological activity. These studies provide a genetic "proof of principle" indicating that inhibitors of prenylation can alter the physiological responses regulated by prenylated proteins.

The Ras protein is part of a signalling pathway that links cell surface growth factor receptors to nuclear signals initiating cellular

- proliferation. Biological and biochemical studies of Ras action indicate that Ras functions like a G-regulatory protein. In the inactive state, Ras is bound to GDP. Upon growth factor receptor activation, Ras is induced to exchange GDP for GTP and undergoes a conformational change. The GTP-bound form of Ras propagates the growth stimulatory signal until the signal is terminated by the intrinsic GTPase activity of Ras, which returns the protein to its inactive GDP bound form (D.R. Lowy and D.M. Willumsen, *Ann. Rev. Biochem.* 62:851-891 (1993)). Activation of Ras leads to activation of multiple intracellular signal transduction pathways, including the MAP Kinase pathway and the Rho/Rac pathway (Joneson *et al.*, *Science* 271:810-812).

- Mutated *ras* genes are found in many human cancers, including colorectal carcinoma, exocrine pancreatic carcinoma, and myeloid leukemias. The protein products of these genes are defective in their GTPase activity and constitutively transmit a growth stimulatory signal.

- The Ras protein is one of several proteins that are known to undergo post-translational prenylation. Farnesyl-protein transferase utilizes farnesyl pyrophosphate to covalently modify the Cys thiol group of the Ras CAAX box with a farnesyl group (Reiss *et al.*, *Cell*, 62:81-88 (1990); Schaber *et al.*, *J. Biol. Chem.*, 265:14701-14704 (1990); Schafer *et al.*, *Science*, 249:1133-1139 (1990); Manne *et al.*, *Proc. Natl. Acad. Sci USA*, 87:7541-7545 (1990)).

- Ras must be localized to the plasma membrane for both normal and oncogenic functions. At least 3 post-translational modifications are involved with Ras membrane localization, and all 3 modifications occur at the C-terminus of Ras. The Ras C-terminus contains a sequence motif termed a "CAAX" or "Cys-Aaa¹-Aaa²-Xaa" box (Cys is cysteine, Aaa is an aliphatic amino acid, the Xaa is any amino acid) (Willumsen *et al.*, *Nature* 310:583-586 (1984)). Depending on the specific sequence, this motif serves as a signal sequence for the enzymes farnesyl-protein transferase or geranylgeranyl-protein transferase, which catalyze the alkylation of the cysteine residue of the CAAX motif with a C₁₅ or C₂₀ isoprenoid, respectively. (S. Clarke.,

Ann. Rev. Biochem. 61:355-386 (1992); W.R. Schafer and J. Rine, *Ann. Rev. Genetics* 30:209-237 (1992)).

Other farnesylated proteins include the Ras-related GTP-binding proteins such as RhoB, fungal mating factors, the nuclear lamins, and the gamma subunit of transducin. James, et al., *J. Biol. Chem.* 269, 14182 (1994) have identified a peroxisome associated protein Pxf which is also farnesylated. James, et al., have also suggested that there are farnesylated proteins of unknown structure and function in addition to those listed above.

- 10 Inhibitors of farnesyl-protein transferase have been described in two general classes. The first class includes analogs of FPP, while the second is related to protein substrates (e.g., Ras) for the enzyme. The peptide derived inhibitors that have been described are generally cysteine containing molecules that are related to the CAAX motif that is the signal for protein prenylation. (Schaber *et al.*, *ibid*;
15 Reiss *et al.*, *ibid*; Reiss *et al.*, *PNAS*, 88:732-736 (1991)). Such inhibitors may inhibit protein prenylation while serving as alternate substrates for the farnesyl-protein transferase enzyme, or may be purely competitive inhibitors (U.S. Patent 5,141,851, University of Texas; N.E. Kohl *et al.*, *Science*, 260:1934-1937 (1993); Graham, et al., *J. Med. Chem.*, 37, 725 (1994)).

- Mammalian cells express four types of Ras proteins (H-, N-, K4A-, and K4B-Ras) among which K-Ras4B is the most frequently mutated form of Ras in human cancers. Inhibition of farnesyl-protein transferase has been shown to block the growth of H-ras-transformed cells in soft agar and to modify other aspects of their transformed phenotype. It has also been demonstrated that certain inhibitors of farnesyl-protein transferase selectively block the processing of the H-Ras oncoprotein intracellularly (N.E. Kohl *et al.*, *Science*, 260:1934-1937 (1993) and G.L. James *et al.*, *Science*, 260:1937-1942 (1993).
25 Recently, it has been shown that an inhibitor of farnesyl-protein transferase blocks the growth of H-ras-dependent tumors in nude mice (N.E. Kohl *et al.*, *Proc. Natl. Acad. Sci. U.S.A.*, 91:9141-9145 (1994)

and induces regression of mammary and salivary carcinomas in H-ras transgenic mice (N.E. Kohl *et al.*, *Nature Medicine*, 1:792-797 (1995).

Indirect inhibition of farnesyl-protein transferase *in vivo* has been demonstrated with lovastatin (Merck & Co., Rahway, NJ)

- 5 and compactin (Hancock *et al.*, *ibid*; Casey *et al.*, *ibid*; Schafer *et al.*, *Science* 245:379 (1989)). These drugs inhibit HMG-CoA reductase, the rate limiting enzyme for the production of polyisoprenoids including farnesyl pyrophosphate. Inhibition of farnesyl pyrophosphate biosynthesis by inhibiting HMG-CoA reductase blocks Ras membrane
10 localization in cultured cells. Because prenyl pyrophosphates are intermediates in many biosynthetic processes, direct inhibition of a prenyl-protein transferase would be more specific and attended by fewer side effects than would occur with the required dose of a general inhibitor of isoprene biosynthesis.

- 15 It is the object of the instant invention to provide a composition that comprises an antineoplastic agent and a prenyl-protein transferase inhibitor whose therapeutic effect in combination may allow use of the antineoplastic agent at a dose which is lower than the dose of the antineoplastic agent if it was used alone and may therefore
20 ameliorate some of the unwanted side effects normally associated with traditional chemotherapy.

- A pharmaceutically effective combination of an antineoplastic agent and a prenyl-protein transferase inhibitor are used in the present invention to treat cancer, such as in tumor cells that are
25 less susceptible to treatment by antagonist of the antineoplastic agent or prenyl-protein transferase inhibitor when administered alone.

SUMMARY OF THE INVENTION

- A method of treating cancer is disclosed which is comprised
30 of administering to a mammalian patient in need of such treatment an effective amount of a combination of an antineoplastic agent and a prenyl-protein transferase inhibitor. Preferably an antineoplastic agent and a farnesyl protein transferase inhibitor are used in such a combination.

35

BRIEF DESCRIPTION OF THE FIGURES

FIGURE 1: Effect of a Farnesyl-protein Transferase Inhibitor in combination with paclitaxel on MCF-7 Cells:

- 5 Cell proliferation of MCF-7 cells (ATCC HTB-22; *J. Natl. Cancer Inst. (Bethesda)* 51:1409-1416 (1973)) which were preincubated for one day in the presence or absence of 0.02 μ M Compound A, followed by a 4 hour treatment with various concentrations of paclitaxel. After the treatment with paclitaxel, the cell were incubated for 7 additional days
- 10 in the presence or absence of 0.02 μ M Compound A. See Protocol B in the "In vitro growth inhibition of human tumor cells assay."

FIGURE 2: Effect of a Farnesyl-protein Transferase Inhibitor in combination with paclitaxel on MDA MB-468 Cells:

- 15 Cell proliferation of MDA MB-468 cells (ATCC HTB-132; *In Vitro (Rockville)* 14:911-915 (1978)) which were treated with various concentrations of paclitaxel for 4 hours. After the treatment with paclitaxel the cell were incubated for 9 days in the absence or presence of 0.2 μ M or 0.5 μ M Compound A. See Protocol A
- 20 in the "In vitro growth inhibition of human tumor cells assay."

FIGURE 2A: Effect of a Farnesyl-protein Transferase Inhibitor in combination with paclitaxel on MDA MB-468 Cells:

- 25 Cell proliferation of MDA MB-468 cells which were pre-incubated in the absence or presence of 0.2 μ M or 0.5 μ M Compound A. At the end of 24 hours the cells were also exposed to various concentrations of paclitaxel for 4 hours. After the treatment with paclitaxel the cell were washed and incubated for 8 days in the presence of the pre-incubation concentration of Compound A. See Protocol B in the
- 30 "In vitro growth inhibition of human tumor cells assay."

FIGURE 2B: Effect of a Farnesyl-protein Transferase Inhibitor in combination with paclitaxel on MDA MB-468 Cells:

Cell proliferation of MDA MB-468 cells were exposed to various concentrations of paclitaxel in the absence or presence of 0.2 μM or 0.5 μM Compound A for 6 days. See Protocol C in the "In vitro growth inhibition of human tumor cells assay."

5

FIGURES 3A and 3B: Effect of a Farnesyl-protein Transferase Inhibitor in combination with paclitaxel on DU145 Cells:

DU145 human prostate cancer cells (ATCC HTB-81, *Cancer Res.* 37:4049-4058 (1977), *Int. J. Cancer*, 21:274-281 (1978)), which were treated for four (4) hours with paclitaxel and then washed, were treated in anchorage-dependent and -independent growth assays in the absence or presence of 0.2 μM , 2 μM or 20 μM Compound A. For Figure 3A, which represents the effect of a combination of paclitaxel and Compound A on anchorage-independent growth, see Protocol D-1 in the "In vitro growth inhibition of human tumor cells assay." For Figure 3B, which represents the effect of a combination of paclitaxel and Compound A on anchorage-dependent growth, see Protocol D-2 in the "In vitro growth inhibition of human tumor cells assay."

20 FIGURES 4 and 4A-4L: Effect of a Farnesyl-protein Transferase Inhibitor in combination with paclitaxel on the cell cycle of MCF-7 Cells:

MCF-7 cells were preincubated for one day, followed by a 24 hour treatment with various concentrations of paclitaxel in the presence or absence of 1 μM Compound A. The DNA contents of the cells were then assessed according to the protocol described in "In vitro cell cycle assay." The cell population having various DNA quantities was then determined and analyzed graphically. Figure 4 shows a composite of 12 cell DNA-content histograms representing the various treatment combinations. Figures 4A-4L show the individual histograms in greater detail. Figures 4A-4F show the histograms of the treatment in the absence of Compound A and with increasing concentrations of paclitaxel (the left column of Figure 4). Figures 4G-4L show the histograms of the treatment in the presence of 1 μM of Compound A and with

increasing concentrations of paclitaxel (the right column of Figure 4). The addition of Compound A increases the molar potency with which paclitaxel causes G₂/M phase arrest in MCF-7 cells.

5 FIGURE 5: Specific Effect of a Farnesyl-protein Transferase Inhibitor in combination with paclitaxel on the cell cycle of MCF-7 Cells:

The cells which contained the doubled DNA content from the assay described above for Figures 4 and 4A-4L were analyzed to determine which particular cell cycle phase was affected by the addition of
10 Compound A to the paclitaxel treatment. Thus, aliquots of the cell populations for the various paclitaxel/Compound A treatments were fixed in 3% paraformaldehyde for 10 minutes, washed in PBS and stained in 24 µg/ml bis-benzimide in PBS. Mitotic cells were distinguished from interphase cells under fluorescence microscopy by
15 characteristic chromatin condensation and mitotic indices were obtained by manual counting of 1000 cells in each experimental treatment group. The results of those counts are shown in Figure 5. The results show that the enhancement in blockage at the G₂/M phase of the cell cycle is largely due to an effect on the M-phase.

20

FIGURE 6: Effect of a Farnesyl-protein Transferase Inhibitor in combination with paclitaxel on DU145 Cells:

Cell proliferation of DU145 cells which were treated with various concentrations of paclitaxel for 4 hours. Cells were seeded 30,000/6
25 well plate. After the treatment with paclitaxel, the cells were incubated for 5 days in the absence or presence of various concentrations of Compound A. See Protocol A in the "In vitro growth inhibition of human tumor cells assay."

30 FIGURE 7: Effect of a Farnesyl-protein Transferase Inhibitor in combination with paclitaxel on T47D Cells:

Cell proliferation of T47D cells which were treated with various concentrations of paclitaxel for 4 hours. Cells were seeded 20,000/6 well plate. After the treatment with paclitaxel, the cells were incubated

for 10 days in the absence or presence of various concentrations of Compound A. See Protocol A in the "In vitro growth inhibition of human tumor cells assay."

- 5 **FIGURE 8: Effect of a Farnesyl-protein Transferase Inhibitor in combination with paclitaxel on MDA-231 Cells:**
Cell proliferation of MDA-231 cells (ATCC HTB-26, *J. Natl. Cancer Inst. (Bethesda)* 53:661-674 (1974)) which were treated with various concentrations of paclitaxel for 4 hours. Cells were seeded 5,000/6 well plate. After the treatment with paclitaxel, the cells were incubated for 7 days in the absence or presence of various concentrations of Compound A. See Protocol A in the "In vitro growth inhibition of human tumor cells assay."
- 10
- 15 **FIGURE 9: Effect of a Farnesyl-protein Transferase Inhibitor in combination with paclitaxel on SK-OV-3 Cells:**
Cell proliferation of SK-OV-3 cells (ATCC HTB-77, *J. Natl. Cancer Inst. (Bethesda)* 58:209-214 (1977)) which were treated with various concentrations of paclitaxel for 4 hours. Cells were seeded 20,000/6 well plate. After the treatment with paclitaxel, the cells were incubated for 4 days in the absence or presence of various concentrations of Compound A. See Protocol A in the "In vitro growth inhibition of human tumor cells assay."
- 20
- 25 **FIGURE 10: Effect of a Farnesyl-protein Transferase Inhibitor in combination with paclitaxel on A549 Cells:**
Cell proliferation of A549 cells (ATCC CCL-185, *J. Natl. Cancer Inst. (Bethesda)* 51:1417-1423 (1973)) which were treated with various concentrations of paclitaxel for 4 hours. Cells were seeded 25,000/6 well plate. After the treatment with paclitaxel, the cells were incubated for 3 days in the absence or presence of various concentrations of Compound A. See Protocol A in the "In vitro growth inhibition of human tumor cells assay."
- 30

FIGURE 11: Effect of a Farnesyl-protein Transferase Inhibitor in combination with paclitaxel on SkBr3 Cells:

Cell proliferation of SkBr3 cells (ATCC HTB-30) which were treated with various concentrations of paclitaxel for 4 hours. Cells were seeded 40,000/6 well plate. After the treatment with paclitaxel, the cells were incubated for 6 days in the absence or presence of various concentrations of Compound A. See Protocol A in the "In vitro growth inhibition of human tumor cells assay."

FIGURE 12: Effect of a Farnesyl-protein Transferase Inhibitor in combination with paclitaxel on PC3 Cells:

Cell proliferation of PC3 cells (ATCC CRL-1435; Invest. Urol., 17:16-23 (1979); Cancer Res. 40: 524-534 (1980)) which were treated with various concentrations of paclitaxel for 4 hours. Cells were seeded 25,000/6 well plate. After the treatment with paclitaxel, the cells were incubated for 5 days in the absence or presence of various concentrations of Compound A. See Protocol A in the "In vitro growth inhibition of human tumor cells assay."

FIGURE 13: Effect of a Farnesyl-protein Transferase Inhibitor in combination with ara-C on MCF-7 Cells:

Cell proliferation of MCF-7 cells which were treated with various concentrations of ara-C for 4 hours. Cells were seeded 20,000/6 well plate. After the treatment with ara-C, the cells were incubated for 7 days in the absence or presence of various concentrations of Compound A. See Protocol A in the "In vitro growth inhibition of human tumor cells assay."

FIGURE 14: Effect of a Farnesyl-protein Transferase Inhibitor in combination with vinblastine on MCF-7 Cells:

Cell proliferation of MCF-7 cells which were treated with various concentrations of vinblastine for 4 hours. Cells were seeded 20,000/6 well plate. After the treatment with vinblastine the cells were incubated for 7 days in the absence or presence of various concentrations of

Compound A. See Protocol A in the "In vitro growth inhibition of human tumor cells assay."

5 FIGURE 15: Effect of a Farnesyl-protein Transferase Inhibitor in combination with 5-fluorouracil on MCF-7 Cells:

Cell proliferation of MCF-7 cells which were treated with various concentrations of 5-fluorouracil for 4 hours. Cells were seeded 20,000/6 well plate. After the treatment with 5-fluorouracil, the cells were incubated for 7 days in the absence or presence of various concentrations of Compound A. See Protocol A in the "In vitro growth inhibition of human tumor cells assay."

15 FIGURE 16: Effect of a Farnesyl-protein Transferase Inhibitor in combination with colchicine on MDA-468 Cells:

Cell proliferation of MDA-468 cells which were treated with various concentrations of colchicine in the absence or presence of various concentrations of Compound A for 24 hours. Cells were seeded 20,000/6 well plate. After the treatment with colchicine and Compound A, the cells were washed and then were incubated for 8 days in the absence or presence of various concentrations of Compound A. See Protocol C in the "In vitro growth inhibition of human tumor cells assay."

25 FIGURE 17: Effect of a Farnesyl-protein Transferase Inhibitor in combination with vinblastine on MCF-7 Cells:

Cell proliferation of MCF-7 cells which were treated with various concentrations of vinblastine for 7 days in the absence or presence of various concentrations of Compound A. Cells were seeded 10,000/6 well plate. See Protocol B in the "In vitro growth inhibition of human tumor cells assay."

30 FIGURE 18: Effect of a Farnesyl-protein Transferase Inhibitor in combination with doxorubicin on MDA-468 Cells:

- Cell proliferation of MDA-468 cells which were treated with various concentrations of doxorubicin for 4 hours. Cells were seeded 20,000/6 well cluster. After the treatment with doxorubicin, the cells were incubated for 10 days in the absence or presence of various concentrations of Compound A. See Protocol A in the "In vitro growth inhibition of human tumor cells assay."

FIGURE 19: Effect of a Farnesyl-protein Transferase Inhibitor in combination with doxorubicin on MCF-7 Cells:

- Cell proliferation of MCF-7 cells which were treated with various concentrations of doxorubicin for 4 hours. Cells were seeded 20,000/6 well cluster. After the treatment with doxorubicin, the cells were incubated for 7 days in the absence or presence of various concentrations of Compound A. See Protocol A in the "In vitro growth inhibition of human tumor cells assay."

FIGURE 20: Effect of a Farnesyl-protein Transferase Inhibitor in combination with cisplatin on MDA-468 Cells:

- Cell proliferation of MDA-468 cells which were treated with various concentrations of cisplatin for 4 hours. Cells were seeded 20,000/6 well cluster. After the treatment with cisplatin, the cells were incubated for 10 days in the absence or presence of various concentrations of Compound A. See Protocol A in the "In vitro growth inhibition of human tumor cells assay."

FIGURE 21: Effect of a Farnesyl-protein Transferase Inhibitor in combination with cisplatin on MCF-7 Cells:

- Cell proliferation of MCF-7 cells which were treated with various concentrations of cisplatin for 4 hours. Cells were seeded 20,000/6 well cluster. After the treatment with cisplatin, the cells were incubated for 7 days in the absence or presence of various concentrations of Compound A. See Protocol A in the "In vitro growth inhibition of human tumor cells assay."

FIGURE 22: *Effect of a Farnesyl-protein Transferase Inhibitor in combination with vinblastine on MDA-468 Cells:*

- Cell proliferation of MDA-468 cells which were treated with various concentrations of vinblastine for 4 hours. Cells were seeded 20,000/6 well cluster. After the treatment with vinblastine, the cells were incubated for 7 days in the absence or presence of various concentrations of Compound A. See Protocol A in the "In vitro growth inhibition of human tumor cells assay."

10 FIGURE 23: *Effect of a Farnesyl-protein Transferase Inhibitor in combination with desoxyepithilone A on MDA-468 Cells:*

- Cell proliferation of MDA-468 cells which were treated with various concentrations of desoxyepithilone A for 4 hours. Cells were seeded 20,000/6 well cluster. After the treatment with desoxyepithilone A, the cells were incubated for 7 days in the absence or presence of various concentrations of Compound A. See Protocol A in the "In vitro growth inhibition of human tumor cells assay."

20 FIGURE 24: *Effect of a Farnesyl-protein Transferase Inhibitor in combination with epithilone A on DU 145 Cells:*

- Cell proliferation of DU 145 cells which were treated with various concentrations of epithilone A for 4 hours. Cells were seeded 20,000/6 well cluster. After the treatment with epithilone A, the cells were incubated for 7 days in the absence or presence of various concentrations of Compound A. See Protocol A in the "In vitro growth inhibition of human tumor cells assay."

FIGURE 25: *Effect of a Farnesyl-protein Transferase Inhibitor in combination with epithilone B on DU 145 Cells:*

- 30 Cell proliferation of DU 145 cells which were treated with various concentrations of epithilone B for 4 hours. Cells were seeded 20,000/6 well cluster. After the treatment with epithilone B, the

cells were incubated for 7 days in the absence or presence of various concentrations of Compound A. See Protocol A in the "In vitro growth inhibition of human tumor cells assay."

- 5 **FIGURE 26: Effect of a Farnesyl-protein Transferase Inhibitor in combination with desoxyepithilone A on DU 145 Cells:**
Cell proliferation of DU 145 cells which were treated with various concentrations of desoxyepithilone A for 4 hours. Cells were seeded 20,000/6 well cluster. After the treatment with desoxyepithilone A, the
10 cells were incubated for 7 days in the absence or presence of various concentrations of Compound A. See Protocol A in the "In vitro growth inhibition of human tumor cells assay."

- 15 **FIGURE 27: Effect of a Farnesyl-protein Transferase Inhibitor in combination with desoxyepithilone B on DU 145 Cells:**
Cell proliferation of DU 145 cells which were treated with various concentrations of desoxyepithilone B for 4 hours. Cells were seeded 20,000/6 well cluster. After the treatment with desoxyepithilone B, the
20 cells were incubated for 7 days in the absence or presence of various concentrations of Compound A. See Protocol A in the "In vitro growth inhibition of human tumor cells assay."

- FIGURE 28: Effect of a Farnesyl-protein Transferase Inhibitor in combination with etoposide on DU 145 Cells:**
25 Cell proliferation of DU 145 cells which were treated with various concentrations of etoposide for 4 hours. Cells were seeded 20,000/6 well cluster. After the treatment with etoposide, the cells were incubated for 7 days in the absence or presence of various concentrations of Compound A. See Protocol A in the "In vitro
30 growth inhibition of human tumor cells assay."

FIGURE 29: Effect of a Farnesyl-protein Transferase Inhibitor in combination with doxorubicin on DU 145 Cells:
Cell proliferation of DU 145 cells which were treated with

- various concentrations of doxorubicin for 4 hours. Cells were seeded 20,000/6 well cluster. After the treatment with doxorubicin, the cells were incubated for 7 days in the absence or presence of various concentrations of Compound A. See Protocol A in the "In vitro growth inhibition of human tumor cells assay."

FIGURE 30: Effect of a Farnesyl-protein Transferase Inhibitor in combination with estramustine on DU 145 Cells:

- Cell proliferation of DU 145 cells which were treated with various concentrations of estramustine for 4 hours. Cells were seeded 20,000/6 well cluster. After the treatment with estramustine, the cells were incubated for 7 days in the absence or presence of various concentrations of Compound A. See Protocol A in the "In vitro growth inhibition of human tumor cells assay."

FIGURE 31: Effect of a Farnesyl-protein Transferase Inhibitor in combination with cis-platinum on DU 145 Cells:

- Cell proliferation of DU 145 cells which were treated with various concentrations of cis-platinum for 4 hours. Cells were seeded 20,000/6 well cluster. After the treatment with cis-platinum, the cells were incubated for 7 days in the absence or presence of various concentrations of Compound A. See Protocol A in the "In vitro growth inhibition of human tumor cells assay."

FIGURE 32: Effect of a Farnesyl-protein Transferase Inhibitor in combination with bicalutamide on LNCaP Cells:

- Cell proliferation of LNCaP cells which were treated with various concentrations of bicalutamide for 4 hours. Cells were seeded 20,000/6 well cluster. After the treatment with bicalutamide, the cells were incubated for 7 days in the absence or presence of various concentrations of Compound A. See Protocol A in the "In vitro growth inhibition of human tumor cells assay."

FIGURE 33: Effect of a Farnesyl-protein Transferase Inhibitor in combination with γ -radiation on DU 145 Cells:

Cell proliferation of DU 145 cells which were treated with various amounts of γ -radiation. Cells were seeded 20,000/6 well cluster. Cells were either pretreated with 20 mM Compound A, treated with 20 mM Compound A after irradiation or not treated with an FTI.

DETAILED DESCRIPTION OF THE INVENTION

- The present invention relates to a method of treating cancer which is comprised of administering to a mammalian patient in need of such treatment an effective amount of a combination of an antineoplastic agent and a prenyl-protein transferase inhibitor. The present method of treating cancer by simultaneously inhibiting protein prenylation and interfering with DNA replication and/or inducing apoptosis offers advantages over previously disclosed methods which utilize a prenyl-protein transferase inhibitor or an antineoplastic agent alone, in that the inhibitory activity and dosage of the instant combination of inhibitors of prenyl-protein transferase and anti-neoplastic agents can be individually varied depending on the nature of the cancer cells to be treated. Any compounds which act as an antineoplastic agent and any compounds which inhibit prenyl-protein transferase can be used in the instant method. Preferably the compounds utilized in the instant combination are an antineoplastic agent and a farnesyl-protein transferase inhibitor. When practicing the present method the antineoplastic agent and the inhibitor of prenyl-protein transferase may be administered either sequentially in any order or simultaneously.

- It is anticipated that the therapeutic effect of the instant compositions may be achieved with smaller amounts of the antineoplastic agents and prenyl-protein transferase inhibitors than would be required if such antineoplastic agents and a prenyl-protein transferase inhibitors were administered alone, thereby avoiding any non-mechanism-based adverse toxicity effects which might result from administration of an amount of the single antineoplastic agent or prenyl-protein transferase inhibitor sufficient to achieve the same therapeutic

effect. It is also anticipated that the instant compositions will achieve a synergistic therapeutic effect or will exhibit unexpected therapeutic advantage over the effect of any of the component compounds if administered alone.

- 5 As used herein the term an antineoplastic agent refers to compounds which either prevent cancer cells from multiplying by interfering with the cell's ability to replicate DNA or induce apoptosis in the cancerous cells.

- 10 The term prenyl-protein transferase inhibiting compound refers to compounds which antagonize, inhibit or counteract the expression of the gene coding a prenyl-protein transferase or the activity of the protein product thereof.

- 15 The term farnesyl protein transferase inhibiting compound likewise refers to compounds which antagonize, inhibit or counteract the expression of the gene coding farnesyl-protein transferase or the activity of the protein product thereof.

- 20 The term selective as used herein refers to the inhibitory activity of the particular compound against a prenyl-protein transferase activity or farnesyl-protein transferase activity. Preferably, for example, a selective inhibitor of farnesyl-protein transferase exhibits at least 20 times greater activity against farnesyl-protein transferase when comparing its activity against another receptor or enzymatic activity, respectively. More preferably the selectivity is at least 100 times or more.

- 25 The extent of selectivity of the two inhibitors that comprise the method of the instant invention may effect the advantages that the method of treatment claimed herein offers over previously disclosed methods of using a single antineoplastic agent or prenyl-protein transferase inhibitor for the treatment of cancer. In particular,
30 use of two independent pharmaceutically active components that have complementary, essentially non-overlapping activities allows the person utilizing the instant method of treatment to independently and accurately vary the inhibitory activity of the combination without having to

synthesize a single drug having a particular pharmaceutical activity profile.

- The term "synergistic" as used herein means that the effect achieved with the methods and compositions of this invention is greater than the sum of the effects that result from methods and compositions comprising the prenyl-protein transferase inhibitor and antineoplastic agent of this invention separately and in the amounts employed in the methods and compositions hereof. Such synergy between the two active ingredients enabling smaller doses to be given and preventing or delaying the build up of multi-drug resistance.

- The preferred therapeutic effect provided by the instant composition is the treatment of cancer and specifically the inhibition of cancerous tumor growth and/or the regression of cancerous tumors. Cancers which are treatable in accordance with the invention described herein include cancers of the brain, breast, colon, genitourinary tract, lymphatic system, pancreas, rectum, stomach, larynx, liver, lung and prostate. More particularly, such cancers include histiocytic lymphoma, lung adenocarcinoma, pancreatic carcinoma, colo-rectal carcinoma, small cell lung cancers and neurological tumors.

- The composition of this invention is also useful for inhibiting other proliferative diseases, both benign and malignant, wherein Ras proteins are aberrantly activated as a result of oncogenic mutation in other genes (i.e., the Ras gene itself is not activated by mutation to an oncogenic form) with said inhibition being accomplished by the administration of an effective amount of the instant composition to a mammal in need of such treatment. For example, a component of NF-1 is a benign proliferative disorder.

- The composition of the instant invention is also useful in the prevention of restenosis after percutaneous transluminal coronary angioplasty by inhibiting neointimal formation (C. Indolfi et al. Nature medicine, 1:541-545(1995).

The instant composition may also be useful in the treatment and prevention of polycystic kidney disease (D.L. Schaffner et al.

American Journal of Pathology, 142:1051-1060 (1993) and B. Cowley, Jr. et al.FASEB Journal, 2:A3160 (1988)).

The pharmaceutical composition of this invention may be administered to mammals, preferably humans, either alone or, preferably, in combination with pharmaceutically acceptable carriers or diluents, optionally with known adjuvants, such as alum, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

For oral use of a chemotherapeutic combination according to this invention, the selected combination or compounds may be administered, for example, in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch, and lubricating agents, such as magnesium stearate, are commonly added. For oral administration in capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredients are combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents may be added. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient are usually prepared, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

The combinations of the instant invention may also be co-administered with other well known therapeutic agents that are selected for their particular usefulness against the condition that is being treated.

If formulated as a fixed dose, such combination products employ the combinations of this invention within the dosage range described below and the other pharmaceutically active agent(s) within its approved dosage range. Combinations of the instant invention may alternatively be used sequentially with known pharmaceutically

acceptable agent(s) when a multiple combination formulation is inappropriate.

The instant invention encompasses a method of treatment wherein an antineoplastic agent and an inhibitor of prenyl-protein transferase are administered simultaneously or sequentially. Thus, while a pharmaceutical formulation comprising an antineoplastic agent and an inhibitor of prenyl-protein transferase may be advantageous for administering the combination for one particular treatment, sequential administration of the components of the combination may be advantageous in another treatment. It is also understood that the instant combination of antineoplastic agent and inhibitor of prenyl-protein transferase may be used in conjunction with other methods of treating cancer and/or tumors, including radiation therapy and surgery.

Radiation therapy, including x-rays or gamma rays which are delivered from either an externally applied beam or by implantation of tiny radioactive sources, may also be used in combination with an inhibitor of prenyl-protein transferase alone to treat cancer. The prenyl-protein transferase inhibitors may either be administered concurrently with the radiation therapy or may be administered prior to the application of the radiation.

In a particularly useful example of the method comprises of combining radiation therapy and administering an inhibitor of prenyl-protein transferase, a farnesyl-protein transferase inhibitor which is:

25 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone isopropyl ester (Compound A);
is administered prior to the application of radiation therapy.

30 In another particularly useful example of the method comprises of combining radiation therapy and administering an inhibitor of prenyl-protein transferase, a farnesyl-protein transferase inhibitor which is:

1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolymethyl]-2-piperazinone;
or a pharmaceutically acceptable salt thereof;
is administered prior to the application of radiation therapy.

5

In another particularly useful example of the method comprises of combining radiation therapy and administering an inhibitor of prenyl-protein transferase, a farnesyl-protein transferase inhibitor which is:

10

(R)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolymethyl]-5-[2-(ethanesulfonyl)methyl]-2-piperazinone;
or a pharmaceutically acceptable salt thereof;
is administered prior to the application of radiation therapy.

15

In another particularly useful example of the method comprises of combining radiation therapy and administering an inhibitor of prenyl-protein transferase, a farnesyl-protein transferase inhibitor which is:

20

4-[1-(5-Chloro-2-oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-pyrrol-2-ylmethyl]-benzonitrile;
or a pharmaceutically acceptable salt thereof;
is administered prior to the application of radiation therapy.

25

In another particularly useful example of the method comprises of combining radiation therapy and administering an inhibitor of prenyl-protein transferase, a farnesyl-protein transferase inhibitor which is:

30

1-[N-(1-(4-cyanobenzyl)-5-imidazolymethyl)-N-(4-cyanobenzyl)amino]-4-(phenoxy)benzene;
or a pharmaceutically acceptable salt thereof;
is administered prior to the application of radiation therapy.

The present invention also encompasses a pharmaceutical composition useful in the treatment of cancer, comprising the administration of a therapeutically effective amount of the combinations of this invention, with or without pharmaceutically acceptable carriers or diluents. Suitable compositions of this invention include aqueous solutions comprising compounds of this invention and pharmacologically acceptable carriers, e.g., saline, at a pH level, e.g., 7.4. The solutions may be introduced into a patient's blood-stream by local bolus injection.

When a combination according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

In one exemplary application, a suitable amount of an antineoplastic agent and a prenyl-protein transferase inhibitor are administered to a mammal undergoing treatment for cancer. Administration occurs in an amount of each type of inhibitor of between about 0.1 mg/kg of body weight to about 60 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day. A particular therapeutic dosage that comprises the instant composition includes from about 0.01mg to about 500mg of an antineoplastic agent and from about 0.01mg to about 500mg of a prenyl-protein transferase inhibitor. Preferably, the dosage comprises from about 1mg to about 100mg of an antineoplastic agent and from about 1mg to about 100mg of a prenyl-protein transferase inhibitor.

Examples of an antineoplastic agent include, in general, microtubule-stabilising agents (such as paclitaxel (also known as Taxol®), docetaxel (also known as Taxotere®), epothilone A, epothilone B, desoxyepothilone A, desoxyepothilone B or their derivatives); microtubule-disruptor agents; alkylating agents, anti-metabolites; a fusel poison; epidophyllotoxin; an antineoplastic enzyme;

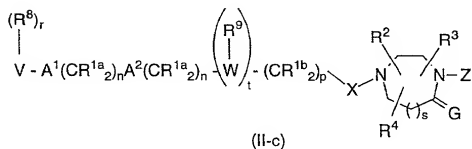
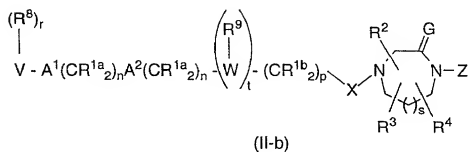
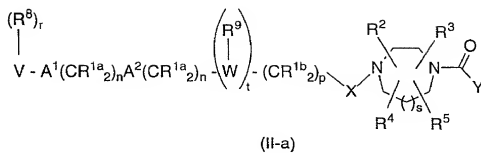
a topoisomerase inhibitor; procarbazine; mitoxantrone; platinum coordination complexes; biological response modifiers and growth inhibitors; hormonal/anti-hormonal therapeutic agents and haematopoietic growth factors.

- 5 Example classes of antineoplastic agents include, for example, the anthracycline family of drugs, the vinca drugs, the mitomycins, the bleomycins, the cytotoxic nucleosides, the taxanes, the epothilones, discodermolide, the pteridine family of drugs, diynes and the podophyllotoxins. Particularly useful members of those classes
- 10 include, for example, doxorubicin, carminomycin, daunorubicin, aminopterin, methotrexate, methopterin, dichloro-methotrexate, mitomycin C, porfiromycin, 5-fluorouracil, 6-mercaptopurine, gemcitabine, cytosine arabinoside, podophyllotoxin or podo-phyllotoxin derivatives such as etoposide, etoposide phosphate or teniposide,
- 15 melphalan, vinblastine, vincristine, leurosine, vindesine, leurosine, paclitaxel and the like. Other useful antineoplastic agents include estramustine, cisplatin, carboplatin, cyclophosphamide, bleomycin, tamoxifen, ifosamide, melphalan, hexamethyl melamine, thiopeta, cytarabin, idatrexate, trimetrexate, dacarbazine, L-asparaginase,
- 20 camptothecin, CPT-11, topotecan, ara-C, bicalutamide, flutamide, leuprolide, pyridobenzoindole derivatives, interferons and interleukins.

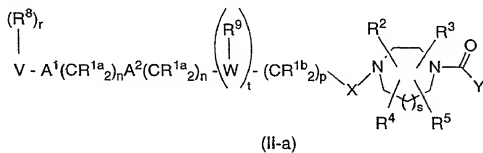
The preferred class of antineoplastic agents is the taxanes and the preferred antineoplastic agent is paclitaxel.

- Examples of farnesyl-protein transferase inhibiting
- 25 compounds include the following:

- (a) a compound represented by formula (II-a) through (II-c):



wherein with respect to formula (II-a):

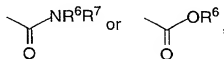


- 5 or a pharmaceutically acceptable salt thereof,

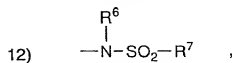
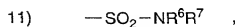
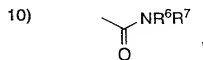
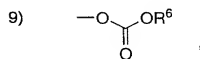
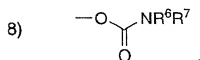
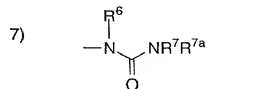
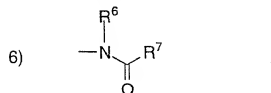
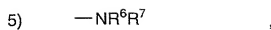
R^{1a} and R^{1b} are independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- 5 c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocyclyl, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃,
 10 -N(R¹⁰)₂, or R¹¹OC(O)-NR¹⁰-;

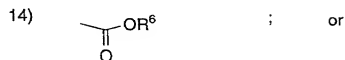
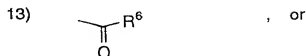
- R² and R³ are independently selected from: H; unsubstituted or substituted C₁-8 alkyl, unsubstituted or substituted C₂-8 alkenyl, unsubstituted or substituted C₂-8 alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle,
- 15



- wherein the substituted group is substituted with one or more of:
- 20 1) aryl or heterocycle, unsubstituted or substituted with:
- a) C₁-4 alkyl,
- b) (CH₂)_pOR⁶,
- c) (CH₂)_pNR⁶R⁷,
- d) halogen,
- 25 2) C₃-6 cycloalkyl,
- 3) OR⁶,
- 4) SR⁶, S(O)R⁶, SO₂R⁶,



5

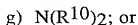
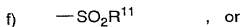
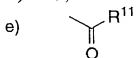


R^2 and R^3 are attached to the same C atom and are combined to form
 - $(\text{CH}_2)_u$ - wherein one of the carbon atoms is optionally replaced by a
 10 moiety selected from: O, S(O)_m , —NC(O)— , and $\text{—N(COR}^{10})\text{—}$;

- R⁴ and R⁵ are independently selected from H and CH₃; and any two of R², R³, R⁴ and R⁵ are optionally attached to the same carbon atom; R⁶, R⁷ and R^{7a} are independently selected from: H; C₁₋₄ alkyl, C₃₋₆ cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

- a) C₁₋₄ alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,

10



- 15 R⁶ and R⁷ may be joined in a ring;

R⁷ and R^{7a} may be joined in a ring;

R⁸ is independently selected from:

- 20 a) hydrogen,
b) aryl, heterocycle, C₃₋₁₀ cycloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, R¹⁰₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or
25 R¹¹OC(O)NR¹⁰-, and
c) C₁₋₆ alkyl unsubstituted or substituted by aryl, heterocycle, C₃₋₁₀ cycloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NH-, CN, H₂N-C(NH)-, R¹⁰C(O)-, R¹⁰OC(O)-,
30 N₃, -N(R¹⁰)₂, or R¹⁰OC(O)NH-;

R⁹ is selected from:

- a) hydrogen,
- b) C₂-C₆ alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br,
 5 R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂,
 (R¹⁰)₂N-C-(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃,
 -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- c) C₁-C₆ alkyl unsubstituted or substituted by perfluoroalkyl,
 10 F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN,
 (R¹⁰)₂N-C-(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃,
 -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

R¹⁰ is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and
 aryl;

15

R¹¹ is independently selected from C₁-C₆ alkyl and aryl;

A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-,
 -C(O)-, -C(O)NR¹⁰-, -NR¹⁰C(O)-, O, -N(R¹⁰)-, -S(O)₂N(R¹⁰)-,

20 -N(R¹⁰)S(O)₂-, or S(O)_m;

V is selected from:

- a) hydrogen,
- b) heterocycle,
- c) aryl,
- d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are
 25 replaced with a heteroatom selected from O, S, and N,
 and
- e) C₂-C₂₀ alkenyl,

30 provided that V is not hydrogen if A¹ is S(O)_m and V is not hydrogen
 if A¹ is a bond, n is 0 and A² is S(O)_m;

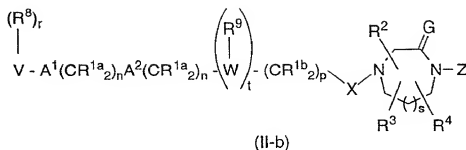
W is a heterocycle;

X is $-\text{CH}_2-$, $-\text{C}(=\text{O})-$, or $-\text{S}(=\text{O})\text{m}-$;

Y is aryl, heterocycle, unsubstituted or substituted with one or
5 more of:

- 1) C_{1-4} alkyl, unsubstituted or substituted with:
 - a) C_{1-4} alkoxy,
 - b) NR^6R^7 ,
 - c) C_{3-6} cycloalkyl,
 - 10 d) aryl or heterocycle,
 - e) HO ,
 - f) $-\text{S}(\text{O})\text{mR}^6$, or
 - g) $-\text{C}(\text{O})\text{NR}^6\text{R}^7$,
 - 2) aryl or heterocycle,
 - 15 3) halogen,
 - 4) OR^6 ,
 - 5) NR^6R^7 ,
 - 6) CN ,
 - 7) NO_2 ,
 - 20 8) CF_3 ;
 - 9) $-\text{S}(\text{O})\text{mR}^6$,
 - 10) $-\text{C}(\text{O})\text{NR}^6\text{R}^7$, or
 - 11) $\text{C}_3\text{-C}_6$ cycloalkyl;
- 25 m is 0, 1 or 2;
 n is 0, 1, 2, 3 or 4;
 p is 0, 1, 2, 3 or 4;
 r is 0 to 5, provided that r is 0 when V is hydrogen;
 s is 0 or 1;
 30 t is 0 or 1; and
 u is 4 or 5;

with respect to formula (II-b):



or a pharmaceutically acceptable salt thereof,

5 R^{1a} , R^{1b} , R^{10} , R^{11} , m , R^2 , R^3 , R^6 , R^7 , p , R^{7a} , u , R^8 , A^1 , A^2 , V , W , X , n , p , r , s , t and u are as defined above with respect to formula (II-a);

R^4 is selected from H and CH_3 ;

10 and any two of R^2 , R^3 and R^4 are optionally attached to the same carbon atom;

R^9 is selected from:

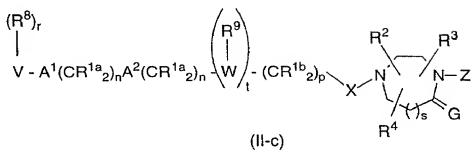
- 15 a) hydrogen,
 b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, $\text{R}^{10}\text{O}-$, $\text{R}^{11}\text{S}(\text{O})_m-$, $\text{R}^{10}\text{C}(\text{O})\text{NR}^{10}-$, CN, NO_2 , $(\text{R}^{10})_2\text{N}-\text{C}(\text{NR}^{10})-$, $\text{R}^{10}\text{C}(\text{O})-$, $\text{R}^{10}\text{OC}(\text{O})-$, N_3 , $-\text{N}(\text{R}^{10})_2$, or $\text{R}^{11}\text{OC}(\text{O})\text{NR}^{10}-$, and
 c) C_1 - C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $\text{R}^{10}\text{O}-$, $\text{R}^{11}\text{S}(\text{O})_m-$, $\text{R}^{10}\text{C}(\text{O})\text{NR}^{10}-$, CN, $(\text{R}^{10})_2\text{N}-\text{C}(\text{NR}^{10})-$, $\text{R}^{10}\text{C}(\text{O})-$, $\text{R}^{10}\text{OC}(\text{O})-$, N_3 , $-\text{N}(\text{R}^{10})_2$, or $\text{R}^{11}\text{OC}(\text{O})\text{NR}^{10}-$;

20 G is H_2 or O ;

25 Z is aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with one or more of the following:
 1) C_{1-4} alkyl, unsubstituted or substituted with:

- | | |
|----|--|
| | a) C1-4 alkoxy, |
| | b) NR ⁶ R ⁷ , |
| | c) C3-6 cycloalkyl, |
| | d) aryl or heterocycle, |
| 5 | e) HO, |
| | f) -S(O) _m R ⁶ , or |
| | g) -C(O)NR ⁶ R ⁷ , |
| | 2) aryl or heterocycle, |
| | 3) halogen, |
| 10 | 4) OR ⁶ , |
| | 5) NR ⁶ R ⁷ , |
| | 6) CN, |
| | 7) NO ₂ , |
| | 8) CF ₃ ; |
| 15 | 9) -S(O) _m R ⁶ , |
| | 10) -C(O)NR ⁶ R ⁷ , or |
| | 11) C3-C6 cycloalkyl; |

with respect to formula (II-c):



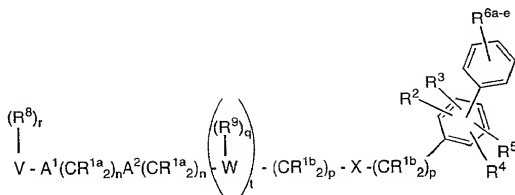
G is O;

- 5 Z is aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with one or more of the following:
- 1) C₁₋₄ alkyl, unsubstituted or substituted with:
 - a) C₁₋₄ alkoxy,
 - b) NR⁶R⁷,
 - 10 c) C₃₋₆ cycloalkyl,
 - d) aryl or heterocycle,
 - e) HO,
 - f) -S(O)_mR⁶, or
 - g) -C(O)NR⁶R⁷,
 - 15 2) aryl or heterocycle,
 - 3) halogen,
 - 4) OR⁶,
 - 5) NR⁶R⁷,
 - 6) CN,
 - 20 7) NO₂,
 - 8) CF₃;
 - 9) -S(O)_mR⁶,
 - 10) -C(O)NR⁶R⁷, or
 - 25 11) C₃-C₆ cycloalkyl;

and

s is 1;

- 30 (b) a compound represented by formula (II-d):



II-d

wherein:

R^{1a} and R^{1b} are independently selected from:

- 5 a) hydrogen,
- b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, R¹¹C(O)O-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, NO₂, R¹⁰C(O)-, N₃-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- 10 c) unsubstituted or substituted C₁-C₆ alkyl wherein the substituent on the substituted C₁-C₆ alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, R¹⁰C(O)-, N₃-, -N(R¹⁰)₂, and R¹¹OC(O)-NR¹⁰-;
- 15

R², R³, R⁴ and R⁵ are independently selected from:


- 20 a) hydrogen,
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, halogen, C₁-C₆ perfluoroalkyl, R¹²O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹¹C(O)O-,

- $R^{10}_2N-C(NR^{10})-$, CN, NO₂, $R^{10}C(O)-$, N₃, $-N(R^{10})_2$,
 or $R^{11}OC(O)NR^{10}-$,
 c) unsubstituted C₁-C₆ alkyl,
 d) substituted C₁-C₆ alkyl wherein the substituent on the
 5 substituted C₁-C₆ alkyl is selected from unsubstituted or
 substituted aryl, unsubstituted or substituted heterocyclic,
 C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl,
 $R^{12}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, $(R^{10})_2NC(O)-$,
 $R^{10}_2N-C(NR^{10})-$, CN, $R^{10}C(O)-$, N₃, $-N(R^{10})_2$, and
 10 $R^{11}OC(O)-NR^{10}-$;

 R^{6a} , R^{6b} , R^{6c} , R^{6d} and R^{6e} are independently selected from:
 a) hydrogen,
 b) unsubstituted or substituted aryl, unsubstituted or
 15 substituted heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl,
 C₂-C₆ alkynyl, halogen, C₁-C₆ perfluoroalkyl, $R^{12}O-$,
 $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, $(R^{10})_2NC(O)-$, $R^{11}C(O)O-$,
 $R^{10}_2N-C(NR^{10})-$, CN, NO₂, $R^{10}C(O)-$, N₃, $-N(R^{10})_2$,
 or $R^{11}OC(O)NR^{10}-$,
 c) unsubstituted C₁-C₆ alkyl,
 d) substituted C₁-C₆ alkyl wherein the substituent on the
 20 substituted C₁-C₆ alkyl is selected from unsubstituted or
 substituted aryl, unsubstituted or substituted heterocyclic,
 C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl,
 25 $R^{12}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, $(R^{10})_2NC(O)-$,
 $R^{10}_2N-C(NR^{10})-$, CN, $R^{10}C(O)-$, N₃, $-N(R^{10})_2$, and
 $R^{11}OC(O)-NR^{10}-$;

 any two of R^{6a} , R^{6b} , R^{6c} , R^{6d} and R^{6e} on adjacent carbon atoms are
 30 combined to form a diradical selected from $-CH=CH-CH=CH-$,
 $-CH=CH-CH_2-$, $-(CH_2)_4-$ and $-(CH_2)_3-$;

R⁷ is selected from: H; C₁₋₄ alkyl, C₃₋₆ cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

- 5
- a) C₁₋₄ alkoxy,
 - b) aryl or heterocycle,
 - c) halogen,
 - d) HO,
 - e) 
 - f) —SO₂R¹¹,
 - g) N(R¹⁰)₂ or
 - h) C₁₋₄ perfluoroalkyl;
- 10

R⁸ is independently selected from:

- 15
- a) hydrogen,
 - b) aryl, substituted aryl, heterocycle, substituted heterocycle, C₃₋₁₀ cycloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, NO₂, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
 - c) C₁₋₆ alkyl unsubstituted or substituted by aryl,
- 20
- cyanophenyl, heterocycle, C₃₋₁₀ cycloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NH-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or R¹⁰OC(O)NH-;
- 25

R⁹ is independently selected from:

- a) hydrogen,
- b) C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-,

$(R^{10})_2NC(O)-$, $R^{10}_2N-C(NR^{10})-$, CN , NO_2 , $R^{10}C(O)-$, N_3 , $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$, and

- c) C₁-C₆ alkyl unsubstituted or substituted by C₁-C₆ perfluoroalkyl, F, Cl, Br, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, $(R^{10})_2NC(O)-$, $R^{10}_2N-C(NR^{10})-$, CN , $R^{10}C(O)-$, N_3 , $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$;

R^{10} is independently selected from hydrogen, C₁-C₆ alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R^{11} is independently selected from C₁-C₆ alkyl and aryl;

R^{12} is independently selected from hydrogen, C₁-C₆ alkyl, C₁-C₆ aralkyl, C₁-C₆ substituted aralkyl, C₁-C₆ heteroaralkyl, C₁-C₆ substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteraryl, C₁-C₆ perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

A^1 and A^2 are independently selected from: a bond, $-CH=CH-$, $-C\equiv C-$, $-C(O)-$, $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, O , $-N(R^{10})-$, $-S(O)_2N(R^{10})-$, $-N(R^{10})S(O)_2-$ or $S(O)_m$;

V is selected from:

- a) hydrogen,
b) heterocycle,
c) aryl,
d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
e) C₂-C₂₀ alkenyl,

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

W is a heterocycle;

X is a bond, $-\text{CH}=\text{CH}-$, O, $-\text{C}(=\text{O})-$, $-\text{C}(\text{O})\text{NR}^7-$, $-\text{NR}^7\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$,
 $-\text{OC}(\text{O})-$, $-\text{C}(\text{O})\text{NR}^7\text{C}(\text{O})-$, $-\text{NR}^7-$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{10})-$,
 $-\text{N}(\text{R}^{10})\text{S}(\text{O})_2-$ or $-\text{S}(=\text{O})_m-$;

m is 0, 1 or 2;

n is independently 0, 1, 2, 3 or 4;

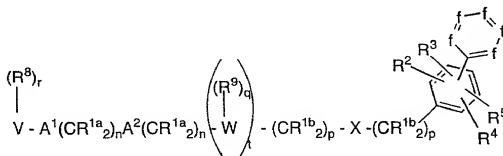
p is independently 0, 1, 2, 3 or 4;

10 q is 0, 1, 2 or 3;

r is 0 to 5, provided that r is 0 when V is hydrogen; and

t is 0 or 1;

(c) a compound represented by formula (II-e):



15

II-e

wherein:

R^{1a} , R^{1b} , R^2 , R^3 , R^4 , R^5 , R^7 , R^8 , R^9 , R^{10} , R^{11} , A^1 , A^2 , V, W, m, n, p,
q, r and t are as previously defined with respect to formula (II-d);

20

from 1-3 of f(s) are independently N, and the remaining f's are
independently CR^6 ; and

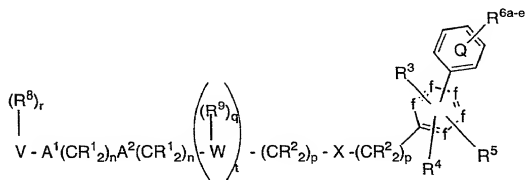
each R^6 is independently selected from:

25

a) hydrogen,

- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, halogen, C₁-C₆ perfluoroalkyl, R¹²O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹¹C(O)O-, R¹⁰₂N-C(NR¹⁰)-, CN, NO₂, R¹⁰C(O)-, N₃-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- 5 c) unsubstituted C₁-C₆ alkyl,
- d) substituted C₁-C₆ alkyl wherein the substituent on the substituted C₁-C₆ alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹²O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, R¹⁰C(O)-, N₃-, -N(R¹⁰)₂, and R¹¹OC(O)-NR¹⁰-, or
- 10 any two of R⁶ on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=, -CH=CH-CH₂-, -(CH₂)₄- and -(CH₂)₃-;

- 20 (d) a compound represented by formula (II-f):



II-f

wherein:

R³, R⁴, R⁵, R⁷, R⁸, R⁹, R¹⁰, R¹¹, A¹, A², V, W, m, n, p, q, r and t are as previously defined with respect to formula (II-d);

from 1-2 of f(s) are independently N, and the remaining f's are
5 independently CH;

from 1-3 of g(s) are independently N, and the remaining g's are independently CR⁶;

10 R¹ and R² are independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, R¹¹C(O)O-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, NO₂,
15 R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- c) unsubstituted or substituted C₁-C₆ alkyl wherein the substituent on the substituted C₁-C₆ alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl,
20 R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, and R¹¹OC(O)-NR¹⁰-; and

each R⁶ is independently selected from:

- 25 a) hydrogen,
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, halogen, C₁-C₆ perfluoroalkyl, R¹²O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹¹C(O)O-,
30 R¹⁰₂N-C(NR¹⁰)-, CN, NO₂, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- c) unsubstituted C₁-C₆ alkyl,
- d) substituted C₁-C₆ alkyl wherein the substituent on the substituted C₁-C₆ alkyl is selected from unsubstituted or

5

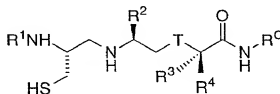
substituted aryl, unsubstituted or substituted heterocyclic, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹²O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, and R¹¹OC(O)-NR¹⁰-; or

10

any two of R⁶ on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH₂-, -(CH₂)₄- and -(CH₂)₃-;

(g)

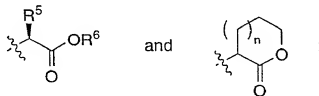
a compound represented by formula (II-h):



II-h

wherein

R^C is selected from:



15

R¹ is hydrogen, an alkyl group, an aralkyl group, an acyl group, an aracyl group, an aroyl group, an alkylsulfonyl group, aralkylsulfonyl group or arylsulfonyl group, wherein alkyl and acyl groups comprise straight chain or branched chain hydrocarbons of 1 to 6 carbon atoms;

20

R² and R³ are

the side chains of naturally occurring amino acids, including their oxidized forms which may be methionine

sulfoxide or methionine sulfone, or in the alternative may be substituted or unsubstituted aliphatic, aromatic or heteroaromatic groups, such as allyl, cyclohexyl, phenyl, pyridyl, imidazolyl or saturated chains of 2 to 8 carbon atoms which may be branched or unbranched, wherein the aliphatic substituents may be substituted with an aromatic or heteroaromatic ring;

R⁴ is hydrogen or an alkyl group, wherein the alkyl group comprises straight chain or branched chain hydrocarbons of 1 to 6 carbon atoms;

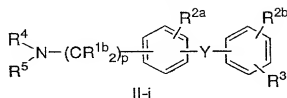
R⁵ is selected from:

- a) a side chain of naturally occurring amino acids,
- b) an oxidized form of a side chain of naturally occurring amino acids selected from methionine sulfoxide and methionine sulfone,
- c) substituted or unsubstituted aliphatic, aromatic or heteroaromatic groups, such as allyl, cyclohexyl, phenyl, pyridyl, imidazolyl, or saturated chains of 2 to 8 carbon atoms which may be branched or unbranched, wherein the aliphatic substituent is optionally substituted with an aromatic or heteroaromatic ring, and
- d) -CH₂CH₂OH or -CH₂CH₂CH₂OH;

R⁶ is a substituted or unsubstituted aliphatic, aromatic or heteroaromatic group such as saturated chains of 1 to 8 carbon atoms, which may be branched or unbranched, wherein the aliphatic substituent may be substituted with an aromatic or heteroaromatic ring;

T is O or S(O)_m;
m is 0, 1 or 2;
n is 0, 1 or 2;

(h) a compound represented by formula (II-i):



wherein:

5

R^{1a} and R^{1b} are independently selected from:

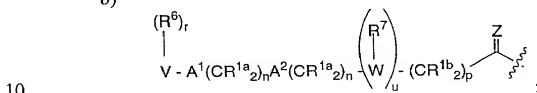
- a) hydrogen,
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C₃-C₆ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R⁸O-, R⁹S(O)_m-, R⁸C(O)NR⁸-, CN, NO₂, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, N₃, -N(R⁸)₂, or R⁹OC(O)NR⁸-,
- 10 c) C₁-C₆ alkyl unsubstituted or substituted by unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, unsubstituted or substituted C₃-C₆ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R⁸O-, R⁹S(O)_m-, R⁸C(O)NR⁸-, CN, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, N₃, -N(R⁸)₂, or R⁹OC(O)-NR⁸-;
- 15
- 20 R^{2a}, R^{2b} and R³ are independently selected from:
 - a) hydrogen,
 - b) C₁-C₆ alkyl unsubstituted or substituted by C₂-C₆ alkenyl, R⁸O-, R⁹S(O)_m-, R⁸C(O)NR⁸-, CN, N₃, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, -N(R⁸)₂, or R⁹OC(O)NR⁸-,
 - 25 c) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted cycloalkyl, alkenyl, R⁸O-, R⁹S(O)_m-, R⁸C(O)NR⁸-, CN, NO₂,

- (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, N₃,
 -N(R⁸)₂, halogen or R⁹OC(O)NR⁸-, and
 d) C₁-C₆ alkyl substituted with an unsubstituted or
 substituted group selected from aryl, heterocyclic and
 C₃-C₁₀ cycloalkyl;

5

R⁴ and R⁵ are independently selected from:

- a) hydrogen, and
 b)



R⁶ is independently selected from:

- a) hydrogen,
 b) unsubstituted or substituted aryl, unsubstituted or
 substituted heterocycle, unsubstituted or substituted C₃-C₆
 cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆
 perfluoroalkyl, F, Cl, Br, R⁸O-, R⁹S(O)_m-, R⁸C(O)NR⁸-,
 CN, NO₂, R⁸₂N-C(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, N₃,
 -N(R⁸)₂, or R⁹OC(O)NR⁸-, and
 c) C₁-C₆ alkyl unsubstituted or substituted by unsubstituted or
 substituted aryl, unsubstituted or substituted heterocycle,
 unsubstituted or substituted C₃-C₆ cycloalkyl, C₂-C₆
 alkenyl, C₂-C₆ alkynyl, C₁-C₆ perfluoroalkyl, F, Cl, Br,
 R⁸O-, R⁹S(O)_m-, R⁸C(O)NH-, CN, H₂N-C(NH)-, R⁸C(O),
 R⁸OC(O)-, N₃, -N(R⁸)₂, or R⁸OC(O)NH-;

25

R⁷ is selected from:

- a) hydrogen,
 b) C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ perfluoroalkyl, F,
 Cl, Br, R⁸O-, R⁹S(O)_m-, R⁸C(O)NR⁸-, CN, NO₂,

30

- (R⁸)₂N-C-(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, N₃, -N(R⁸)₂, or R⁹OC(O)NR⁸-, and
- c) C₁-C₆ alkyl unsubstituted or substituted by C₁-C₆ perfluoroalkyl, F, Cl, Br, R⁸O-, R⁹S(O)_m-, R⁸C(O)NR⁸-, CN, (R⁸)₂N-C-(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, N₃, -N(R⁸)₂, or R⁹OC(O)NR⁸-;

R⁸ is independently selected from hydrogen, C₁-C₆ alkyl, substituted or unsubstituted C₁-C₆ aralkyl and substituted or unsubstituted aryl;

R⁹ is independently selected from C₁-C₆ alkyl and aryl;

R¹⁰ is independently selected from hydrogen, C₁-C₆ alkyl, substituted or unsubstituted C₁-C₆ aralkyl and substituted or unsubstituted aryl;

A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR⁸-, -NR⁸C(O)-, O, -N(R⁸)-, -S(O)₂N(R⁸)-, -N(R⁸)S(O)₂-, or S(O)_m;

V is selected from:

- a) hydrogen,
 - b) heterocycle,
 - c) aryl,
 - d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
 - e) C₂-C₂₀ alkenyl,
- provided that V is not hydrogen if A¹ is S(O)_m and V is not hydrogen if A¹ is a bond, n is 0 and A² is S(O)_m;

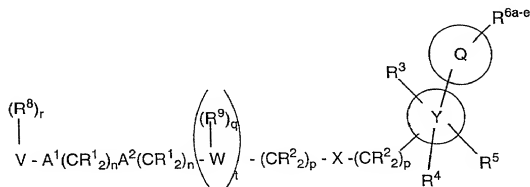
W is a heterocycle;

- Y is selected from: a bond, $-C(R^{10})=C(R^{10})-$, $-C\equiv C-$, $-C(O)-$,
 $-C(R^{10})_2-$, $-C(OR^{10})R^{10}-$, $-CN(R^{10})_2R^{10}-$, $-OC(R^{10})_2-$,
 $NR^{10}C(R^{10})_2-$, $-C(R^{10})_2O-$, $-C(R^{10})_2NR^{10}-$, $-C(O)NR^{10}-$,
 5 $NR^{10}C(O)-$, O, $-NC(O)R^{10}-$, $-NC(O)OR^{10}-$, $-S(O)_2N(R^{10})-$,
 $N(R^{10})S(O)_2-$, or $S(O)_m$;

Z is H_2 or O;

- 10 m is 0, 1 or 2;
 n is 0, 1, 2, 3 or 4;
 p is 0, 1, 2, 3 or 4;
 r is 0 to 5, provided that r is 0 when V is hydrogen; and
 u is 0 or 1;

- 15 (e) a compound represented by formula (II-m):



II-m

wherein:

- 20 Q is a 4, 5, 6 or 7 membered heterocyclic ring which comprises a nitrogen atom through which Q is attached to Y and 0-2 additional heteroatoms selected from N, S and O, and which also comprises a carbonyl, thiocarbonyl, $-C(=NR^{13})-$ or sulfonyl moiety adjacent to the nitrogen atom attached to Y;

- Y is a 5, 6 or 7 membered carbocyclic ring wherein from 0 to 3 carbon atoms are replaced by a heteroatom selected from N, S and O, and wherein Y is attached to Q through a carbon atom;

R¹ and R² are independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, R¹¹C(O)O-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, NO₂, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- c) unsubstituted or substituted C₁-C₆ alkyl wherein the substituent on the substituted C₁-C₆ alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, and R¹¹OC(O)NR¹⁰-;

R³, R⁴ and R⁵ are independently selected from:

- a) hydrogen,
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, halogen, C₁-C₆ perfluoroalkyl, R¹²O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹¹C(O)O-, R¹⁰₂N-C(NR¹⁰)-, CN, NO₂, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- c) unsubstituted C₁-C₆ alkyl,
- d) substituted C₁-C₆ alkyl wherein the substituent on the substituted C₁-C₆ alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl,

$R^{12}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, $(R^{10})_2NC(O)-$,
 $R^{10}_2N-C(NR^{10})-$, CN , $R^{10}C(O)-$, N_3 , $-N(R^{10})_2$, and
 $R^{11}OC(O)-NR^{10}-$;

5 R^{6a} , R^{6b} , R^{6c} , R^{6d} and R^{6e} are independently selected from:

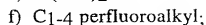
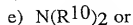
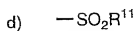
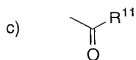
- a) hydrogen,
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C3-C10 cycloalkyl, C2-C6 alkenyl, C2-C6 alkynyl, halogen, C1-C6 perfluoroalkyl,
- 10 $R^{12}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, $(R^{10})_2NC(O)-$,
 $R^{11}S(O)_2NR^{10}-$, $(R^{10})_2NS(O)_2-$, $R^{11}C(O)O-$,
 $R^{10}_2N-C(NR^{10})-$, CN , NO_2 , $R^{10}C(O)-$, N_3 , $-N(R^{10})_2$,
or $R^{11}OC(O)NR^{10}-$,
- c) unsubstituted C1-C6 alkyl,
- 15 d) substituted C1-C6 alkyl wherein the substituent on the substituted C1-C6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C3-C10 cycloalkyl, C2-C6 alkenyl, C2-C6 alkynyl, $R^{12}O-$,
 $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, $(R^{10})_2NC(O)-$,
20 $R^{11}S(O)_2NR^{10}-$, $(R^{10})_2NS(O)_2-$, $R^{10}_2N-C(NR^{10})-$, CN ,
 $R^{10}C(O)-$, N_3 , $-N(R^{10})_2$, and $R^{11}OC(O)-NR^{10}-$; or

any two of R^{6a} , R^{6b} , R^{6c} , R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from $-CH=CH-CH=CH-$, $-CH=CH-CH_2-$, $-(CH_2)_4-$ and $-(CH_2)_3-$;

25

R^7 is selected from: H; C1-4 alkyl, C3-6 cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

- 30 a) C1-4 alkoxy,
- b) aryl or heterocycle,



5 R⁸ is independently selected from:

- a) hydrogen,
- b) aryl, substituted aryl, heterocycle, substituted heterocycle, C3-C10 cycloalkyl, C2-C6 alkenyl, C2-C6 alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹¹S(O)₂NR¹⁰-, (R¹⁰)₂NS(O)₂-, R¹⁰₂N-C(NR¹⁰)-, CN, NO₂, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- 10 c) C1-C6 alkyl unsubstituted or substituted by aryl, cyanophenyl, heterocycle, C3-C10 cycloalkyl, C2-C6 alkenyl, C2-C6 alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹¹S(O)₂NR¹⁰-, (R¹⁰)₂NS(O)₂-, R¹⁰₂N-C(NR¹⁰)-, CN, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or R¹⁰OC(O)NH-;
- 15

20 R⁹ is independently selected from:

- a) hydrogen,
- b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, NO₂, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- 25 c) C1-C6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

R¹⁰ is independently selected from hydrogen, C₁-C₆ alkyl, benzyl, 2,2,2-trifluoroethyl and aryl;

5 R¹¹ is independently selected from C₁-C₆ alkyl and aryl;

10 R¹² is independently selected from hydrogen, C₁-C₆ alkyl, C₁-C₆ aralkyl, C₁-C₆ substituted aralkyl, C₁-C₆ heteroaralkyl, C₁-C₆ substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteraryl, C₁-C₆ perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

15 R¹³ is selected from hydrogen, C₁-C₆ alkyl, cyano, C₁-C₆ alkylsulfonyl and C₁-C₆ acyl;

A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR¹⁰-, -NR¹⁰C(O)-, O, -N(R¹⁰)-, -S(O)₂N(R¹⁰)-, -N(R¹⁰)S(O)₂-, or S(O)_m;

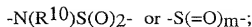
20 V is selected from:

- a) hydrogen,
- b) heterocycle,
- c) aryl,
- d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
- 25 e) C₂-C₂₀ alkenyl,

provided that V is not hydrogen if A¹ is S(O)_m and V is not hydrogen if A¹ is a bond, n is 0 and A² is S(O)_m;

30 W is a heterocycle;

X is a bond, -CH=CH-, O, -C(=O)-, -C(O)NR⁷-, -NR⁷C(O)-, -C(O)O-, -OC(O)-, -C(O)NR⁷C(O)-, -NR⁷-, -S(O)₂N(R¹⁰)-,



m is 0, 1 or 2;

n is independently 0, 1, 2, 3 or 4;

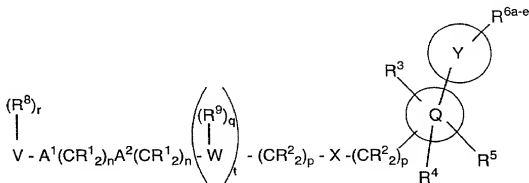
5 p is independently 0, 1, 2, 3 or 4;

q is 0, 1, 2 or 3;

r is 0 to 5, provided that r is 0 when V is hydrogen; and

t is 0 or 1;

10 (f) a compound represented by formula (II-n):



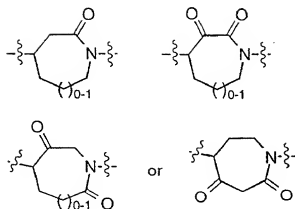
11-n

wherein:

 $R^1, R^2, R^3, R^4, R^5, R^{6a-e}, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, A^1, A^2, V,$

15 W, m, n, p, q, r and t are as previously defined with respect to formula (II-m);

Q is a 4, 5, 6 or 7 membered heterocyclic ring which comprises a nitrogen atom through which Q is attached to Y and 0-2 additional heteroatoms selected from N, S and O, and which also comprises a carbonyl, thiocarbonyl, -C(=NR¹³)- or sulfonyl moiety adjacent to the nitrogen atom attached to Y, provided that Q is not



Y is a 5, 6 or 7 membered carbocyclic ring wherein from 0 to 3 carbon atoms are replaced by a heteroatom selected from N, S and O, and wherein Y is attached to Q through a carbon atom;

or a pharmaceutically acceptable salt or disulfide thereof.

10

Examples of compounds which selectively inhibit farnesyl protein transferase include the following:

2(S)-Butyl-1-(2,3-diaminoprop-1-yl)-1-(1-naphthoyl)piperazine;

15 1-(3-Amino-2-(2-naphthylmethylamino)prop-1-yl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

2(S)-Butyl-1-{5-[1-(2-naphthylmethyl)]-4,5-dihydroimidazol}methyl-4-(1-naphthoyl)piperazine;

20

1-[5-(1-Benzylimidazol)methyl]-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-{5-[1-(4-nitrobenzyl)]imidazolylmethyl}-2(S)-butyl-4-(1-naphthoyl)piperazine;

25

1-(3-Acetamidomethylthio-2(R)-aminoprop-1-yl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

2(S)-Butyl-1-[2-(1-imidazolyl)ethyl]sulfonyl-4-(1-naphthoyl)piperazine;

2(R)-Butyl-1-imidazolyl-4-methyl-4-(1-naphthoyl)piperazine;

5

2(S)-Butyl-4-(1-naphthoyl)-1-(3-pyridylmethyl)piperazine;

1-2(S)-butyl-(2(R)-(4-nitrobenzyl)amino-3-hydroxypropyl)-4-(1-naphthoyl)piperazine;

10

1-(2(R)-Amino-3-hydroxyheptadecyl)-2(S)-butyl-4-(1-naphthoyl)-piperazine;

2(S)-Benzyl-1-imidazolyl-4-methyl-4-(1-naphthoyl)piperazine;

15

1-(2(R)-Amino-3-(3-benzylthio)propyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-(2(R)-Amino-3-[3-(4-nitrobenzylthio)propyl])-2(S)-butyl-4-(1-naphthoyl)piperazine;

20

2(S)-Butyl-1-[(4-imidazolyl)ethyl]-4-(1-naphthoyl)piperazine;

2(S)-Butyl-1-[(4-imidazolyl)methyl]-4-(1-naphthoyl)piperazine;

25

2(S)-Butyl-1-[(1-naphth-2-ylmethyl)-1H-imidazol-5-yl]acetyl]-4-(1-naphthoyl)piperazine;

2(S)-Butyl-1-[(1-naphth-2-ylmethyl)-1H-imidazol-5-yl)ethyl]-4-(1-naphthoyl)piperazine;

30

1-(2(R)-Amino-3-hydroxypropyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-(2(R)-Amino-4-hydroxybutyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

- 1-(2-Amino-3-(2-benzyloxyphenyl)propyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;
- 5 1-(2-Amino-3-(2-hydroxyphenyl)propyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;
- 1-[3-(4-imidazolyl)propyl]-2(S)-butyl-4-(1-naphthoyl)-piperazine;
- 10 2(S)-*n*-Butyl-4-(2,3-dimethylphenyl)-1-(4-imidazolymethyl)-piperazin-5-one;
- 2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-4-(2,3-dimethylphenyl)piperazin-5-one;
- 15 1-[1-(4-Cyanobenzyl)imidazol-5-ylmethyl]-4-(2,3-dimethylphenyl)-2(S)-(2-methoxyethyl)piperazin-5-one;
- 2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(1-naphthylmethyl)imidazol-5-ylmethyl]-piperazine;
- 20 2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(2-naphthylmethyl)imidazol-5-ylmethyl]-piperazine;
- 2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;
- 25 2(S)-*n*-Butyl-1-[1-(4-methoxybenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;
- 30 2(S)-*n*-Butyl-1-[1-(3-methyl-2-butenyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;

- 2(S)-*n*-Butyl-1-[1-(4-fluorobenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;
- 5 2(S)-*n*-Butyl-1-[1-(4-chlorobenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;
- 1-[1-(4-Bromobenzyl)imidazol-5-ylmethyl]-2(S)-*n*-butyl-4-(1-naphthoyl)piperazine;
- 10 2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(4-trifluoromethylbenzyl)imidazol-5-ylmethyl]-piperazine;
- 2(S)-*n*-Butyl-1-[1-(4-methylbenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)-piperazine;
- 15 2(S)-*n*-Butyl-1-[1-(3-methylbenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)-piperazine;
- 1-[1-(4-Phenylbenzyl)imidazol-5-ylmethyl]-2(S)-*n*-butyl-4-(1-naphthoyl)-piperazine;
- 20 2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(2-phenylethyl)imidazol-5-ylmethyl]-piperazine;
- 2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(4-trifluoromethoxy)imidazol-5-ylmethyl]piperazine;
- 25 1-[[1-(4-cyanobenzyl)-1H-imidazol-5-yl]acetyl]-2(S)-*n*-butyl-4-(1-naphthoyl)piperazine;
- 30 (S)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(methanesulfonyl)ethyl]-2-piperazinone;
- (S)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)ethyl]-2-piperazinone;
- 35

(R)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)methyl]-2-piperazinone;

- 5 (S)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[N-ethyl-2-acetamido]-2-piperazinone;

(±)-5-(2-Butynyl)-1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone;

10

1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone;

5(S)-Butyl-4-[1-(4-cyanobenzyl-2-methyl)-5-imidazolylmethyl]-1-(2,3-dimethylphenyl)-piperazin-2-one;

15

4-[1-(2-(4-Cyanophenyl)-2-propyl)-5-imidazolylmethyl]-1-(3-chlorophenyl)-5(S)-(2-methylsulfonylethyl)piperazin-2-one;

20

5(S)-n-Butyl-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-1-(2-methylphenyl)piperazin-2-one;

4-[1-(4-Cyanobenzyl)-5-imidazolylmethyl]-5(S)-(2-fluoroethyl)-1-(3-chlorophenyl)piperazin-2-one;

25

4-[3-(4-Cyanobenzyl)pyridin-4-yl]-1-(3-chlorophenyl)-5(S)-(2-methylsulfonylethyl)-piperazin-2-one;

4-[5-(4-Cyanobenzyl)-1-imidazolethyl]-1-(3-chlorophenyl)piperazin-2-one;

30

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-homoserine lactone,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-homoserine,

35

- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-2-methyl-3-phenylpropionyl-homoserine lactone,
- 5 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-2-methyl-3-phenylpropionyl-homoserine,
- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-4-pentenoyl-homoserine lactone,
- 10 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-pentyloxy-4-pentenoyl-homoserine,
- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxypentanoyl-homoserine lactone,
- 15 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxypentanoyl-homoserine,
- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]5-pentyloxy-4-methylpentanoyl-homoserine lactone,
- 20 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-4-methylpentanoyl-homoserine,
- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-methylbutanoyl-homoserine lactone,
- 25 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-methylbutanoyl-homoserine,
- 30 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-phenylbutanoyl-homoserine lactone,
- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-

pentyloxy-3-phenylbutanoyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentylthio-2-methyl-3-phenylpropionyl-homoserine lactone,

5

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentylthio-2-methyl-3-phenylpropionyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-

10

methyl]pentylsulfonyl-2-methyl-3-phenylpropionyl-homoserine lactone,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-pentylsulfonyl-2-methyl-3-phenylpropionyl-homoserine,

15

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine methyl ester,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-methionine,

20

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-methionine sulfone methyl ester (Compound 5),

25

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-methionine sulfone (Compound 6),

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone isopropyl ester,

30

2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-pentyloxy-3-naphth-2-yl-propionyl-methionine sulfone methyl ester,

2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-

pentyloxy-3-naphth-2-yl-propionyl-methionine sulfone,

- 2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-naphth-1-yl-propionyl-methionine sulfone methyl ester,

2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-naphth-1-yl-propionyl-methionine sulfone,

- 10 2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-methylbutanoyl-methionine methyl ester.

2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-methylbutanoyl-methionine,

- 15 Disulphide of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)methyl]pentyloxy-3-phenylpropionyl-homoserine lactone,

- 20 Disulphide of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-homoserine,

Disulphide of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)methyl]pentyloxy-3-methylbutanoyl-methionine methyl ester

- 25 1-(4-Biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(4-Cyanobenzyl)-5-(4'-phenylbenzamido)ethyl-imidazole

- 30 1-(2'-Trifluoromethyl-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(4-Biphenylethyl)-5-(4-cyanobenzyl)imidazole

- 1-(2'-Bromo-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole
- 5 1-(2'-Methyl-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole
- 1-(2'-Trifluoromethoxy-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole
- 10 1-(4-(3',5'-dichloro)-biphenylmethyl)-5-(4-cyanobenzyl) imidazole
- 1-(2'-Methoxy-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole
- 15 1-(2'-Chloro-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole
- 20 1-(2-Chloro-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole
- 1-(3-Chloro-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole
- 25 1-(4-(3',5'-Bis-trifluoromethyl)-biphenylmethyl)-5-(4-cyanobenzyl)
imidazole
- 30 1-(2'-Trifluoromethyl-4-biphenylmethyl)-5-(4-cyanobenzyl)-4-
methylimidazole
- 1-(4-Biphenylmethyl)-5-(4-cyanophenyl)-imidazole

- 5-(4-Cyanophenoxy)-1-(2'-methyl-4-biphenylmethyl)-imidazole
- 5 5-(4-Biphenyloxy)-1-(4-cyanobenzyl)-imidazole
- 5-(2'-Methyl-4-biphenoxy)-1-(4-cyanobenzyl)-imidazole
- 10 5-(4-(3',5'-dichloro)biphenylmethyl)-1-(4-cyanobenzyl)imidazole
- 15 1-(4-biphenylmethyl)-5-(1-(R,S)-acetoxy-1-(4-cyanophenyl)methylimidazole
- 20 1-(4-Biphenylmethyl)-5-(1-(R,S)-hydroxy-1-(4-cyanophenyl)methylimidazole
- 25 1-(4-Biphenylmethyl)-5-(1-(R,S)-amino-1-(4-cyanophenyl)methylimidazole
- 30 1-(4-Cyanobenzyl)-5-(1-hydroxy-1-(4-biphenyl)-methyl imidazole
- 1-(4-Cyanobenzyl)-5-(1-oxo-1-(4-biphenyl)-methyl imidazole

1-(4-Cyanobenzyl)-5-(1-hydroxy-1-(3-fluoro-4-biphenyl)-methyl)-imidazole

5 1-(4-Cyanobenzyl)-5-(1-hydroxy-1-(3-biphenyl)methyl)-imidazole

5-(2-[1,1'-Biphenyl]vinylene)-1-(4-cyanobenzyl)imidazole

10 1-[N-(1-(4-cyanobenzyl)-5-imidazolylmethyl)amino]-3-methoxy-4-phenylbenzene

1-(4-Biphenylmethyl)-5-(4-bromophenyl)-imidazole

15

1-(3'-Methyl-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

20

1-(4'-Methyl-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(3'-Trifluoromethyl-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

25

1-(4'-Trifluoromethyl-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

30 1-(3'-Chloro-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(4'-Chloro-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

35

1-(2'3'-Dichloro-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

5 1-(2'4'-Dichloro-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(2'5'-Dichloro-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

10 1-(3'-Trifluoromethoxy-4-biphenylmethyl)-5-(4-cyanobenzyl)
imidazole

15 1-(2'-Fluoro-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(4-(2'-Trifluoromethylphenyl)-2-Chlorophenylmethyl)-5-(4-
cyanobenzyl) imidazole

20 1-{1-(4-(2'-trifluoromethylphenyl)phenyl)ethyl}-5-(4-cyanobenzyl)
imidazole

25 1-(2'-Trifluoromethyl-4-biphenylpropyl)-5-(4-cyanobenzyl)
imidazole

1-(2'-N-t-Butoxycarbonylamino-4-biphenylmethyl)-5-(4-
cyanobenzyl) imidazole

30 1-(2'-Aminomethyl-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(2'-Acetylaminomethyl-4-biphenylmethyl)-5-(4-cyanobenzyl)
imidazole

35

- 1-(2'-Methylsulfonylaminomethyl-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole
- 5 1-(2'-Ethylaminomethyl-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole
- 1-(2'-Phenylaminomethyl-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole
- 10 1-(2'-Glycylaminomethyl-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole
- 15 1-(2'-Methyl-4-biphenylmethyl)-2-chloro-5-(4-cyanobenzyl) imidazole
- 1-(2'-Methyl-4-biphenylmethyl)-4-chloro-5-(4-cyanobenzyl) imidazole
- 20 1-(3'-Chloro-2-methyl-4-biphenylmethyl)-4-(4-cyanobenzyl)imidazole
- 1-(3'-Chloro-2-methyl-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole
- 25 1-(3'-Trifluoromethyl-2-methyl-4-biphenylmethyl)-4-(4-cyanobenzyl) imidazole
- 30 1-(3'-Trifluoromethyl-2-methyl-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole
- 35 1-(3'-Methoxy-2-methyl-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(2'-Chloro-4'-fluoro-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

5

1-(2'-Ethyl-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

10 1-(2'-(2-Propyl)-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(2'-(2-Methyl-2-propyl)-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

15

1-(2'-Ethyl-4-biphenylmethyl)-5-(4-(1*H*-tetrazol-5-yl))benzyl)imidazole

20

1-[1-(4-Cyanobenzyl)imidazol-5-ylmethoxy]-4-(2'-methylphenyl)-2-(3-*N*-phthalimido-1-propyl)benzene

25 1-(3',5'-Ditrifluoromethyl-2-methyl-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

30 1-(3',5'-Chloro-2-methyl-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(3',5'-Dimethyl-2-methyl-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(3-(N-Boc-aminomethyl)-4-biphenylmethyl)-5-(4-cyanobenzyl)-
imidazole

5

1-(3-Aminomethyl-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

10 1-(4-Cyanobenzyl)-2-methyl-5-(2'-methylbiphenyl-4-
yloxy)imidazole

15 5-(4-Cyanobenzyl)-1-(3-cyano-2'-trifluoromethylbiphenyl-4-ylmethyl)-
imidazole

2-Amino-5-(biphenyl-4-ylmethyl)-1-(4-cyanobenzyl)imidazole

20

2-Amino-1-(biphenyl-4-ylmethyl)-5-(4-cyanobenzyl)imidazole

1-(3-Butylbiphenyl-4-ylmethyl)-5-(4-cyanobenzyl)-imidazole

25

1-(3-Propylbiphenyl-4-ylmethyl)-5-(4-cyanobenzyl)-imidazole

30 1-(4-Biphenylmethyl)-4-(4-cyanobenzyl-2-methylimidazole

1-(4-Cyanobenzyl)-5-[(3-fluoro-4-biphenyl)methyl]imidazole

35

1-(4-Cyanobenzyl)-5-[1-(4-biphenyl)-1-hydroxy]ethyl-2-methylimidazole

5 1-(4-Cyanobenzyl)-5-(4-biphenylmethyl)-2-methylimidazole

1-(4-Cyanobenzyl)-5-[1-(4-biphenyl)]ethyl-2-methyl imidazole

10

1-(4-Cyanobenzyl)-5-[1-(4-biphenyl)]vinylidene-2-methylimidazole
and

15 1-(4-Cyanobenzyl)-5-[2-(4-biphenyl)]vinylene-2-methylimidazole

1-(4-[Pyrid-2-yl]phenylmethyl)-5-(4-cyanobenzyl)imidazole

20 1-(4-[3-Methylpyrazin-2-yl]phenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(4-(Pyrimidinyl-5-yl)phenylmethyl)-5-(4-cyanobenzyl)imidazole

25

1-(2-Phenylpyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole

1-(2-Phenyl-N-Oxopyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole

1-(3-Phenylpyrid-6-ylmethyl)-5-(4-cyanobenzyl)imidazole

30 1-(3-Phenyl-N-Oxopyrid-6-ylmethyl)-5-(4-cyanobenzyl)imidazole

1-(2-(3-Trifluoromethoxyphenyl)-pyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole

35

- 1-(2-(2-Trifluoromethylphenyl)-pyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole
- 5 1-(3-Phenyl-2-Chloropyrid-6-ylmethyl)-5-(4-cyanobenzyl)imidazole
1-(3-Phenyl-4-chloropyrid-6-ylmethyl)-5-(4-cyanobenzyl)imidazole
- 1-(2-Amino-3-phenylpyrid-6-ylmethyl)-5-(4-cyanobenzyl)imidazole
- 10 1-(2-[Pyrid-2-yl]pyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole
- N-{1-(4-Cyanobenzyl)-1H-imidazol-5-yl)methyl}-5-(pyrid-2-yl)-2-amino-pyrimidine
- N,N*-bis(4-Imidazolemethyl)amino-3-[(3-carboxyphenyl)oxy]benzene
- 15 *N,N*-bis(4-Imidazolemethyl)amino-4-[(3-carboxyphenyl)oxy]benzene
- N,N*-bis(4-Imidazolemethyl)amino-3-[(3-carbomethoxyphenyl)-oxy]benzene
- 20 *N,N*-bis(4-Imidazolemethyl)amino-4-[(3-carbomethoxyphenyl)-oxy]benzene
- N*-(4-Imidazolemethyl)-*N*-(4-nitrobenzyl)aminomethyl-3-[(3-carboxyphenyl)oxy]benzene
- 25 *N*-(4-Imidazolemethyl)-*N*-(4-nitrobenzyl)aminomethyl-3-[(3-carbomethoxyphenyl)oxy]benzene
- 30 *N*-(4-Imidazolemethyl)-*N*-(4-nitrobenzyl)amino-3-(phenoxy)benzene
- N*-(4-Imidazolemethyl)-*N*-(4-nitrobenzyl)amino-4-(phenoxy)benzene
- N*-(4-Imidazolemethyl)-*N*-(4-nitrobenzyl)amino-4-(phenylthio)benzene
- 35

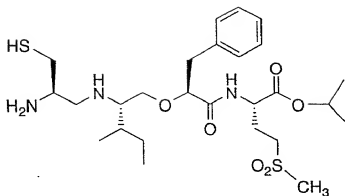
- N*-Butyl-*N*-[1-(4-cyanobenzyl)-5-imidazolomethyl]amino-4-(phenoxy)benzene
- 5 *N*-[1-(4-Cyanobenzyl)-5-imidazolomethyl]amino-4-(phenoxy)benzene
- N*-(4-Imidazolomethyl)amino-3-[(3-carboxyphenyl)oxy]benzene
- 10 1-[*N*-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-*N*-(4-cyanobenzyl)amino]-4-(phenoxy)benzene
- (±)-4-[(4-imidazolylmethyl)amino]pentyl-1-(phenoxy)benzene
- 15 1-[(*N*-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-*N*-(*n*-butyl)amino)methyl]-4-(phenoxy)benzene
- 4-[*N*-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-*N*-(*n*-butyl)amino]-1-(phenylthio)benzene
- 20 (±)-4-[*N*-(1-(4-cyanobenzyl)-4-imidazolylmethyl)-*N*-(*n*-butyl)amino]-1-(phenylsulfinyl)benzene
- 3-[*N*-(4-imidazolylmethyl)-*N*-(*n*-butyl)amino]-*N*-(phenyl)benzenesulfonamide and
- 25 1-[*N*-(1-(4-cyanobenzyl)-5-imidazolylmethyl)amino]-3-methoxy-4-phenylbenzene
- 4-{3-[4-(2-Oxo-2-*H*-pyridin-1-yl)benzyl]-3-*H*-imidazol-4-ylmethyl}benzonitrile
- 30 4-{3-[4-3-Methyl-2-oxo-2-*H*-pyridin-1-yl)benzyl]-3-*H*-imidazol-4-ylmethyl}benzonitrile
- 4-{3-[4-(2-Oxo-piperidin-1-yl)benzyl]-3-*H*-imidazol-4-ylmethyl}benzonitrile
- 35

- 4-{3-[3-Methyl-4-(2-oxopiperidin-1-yl)-benzyl]-3-H-imidazol-4-ylmethyl}-benzonitrile
- 5 4-{3-[4-(2-Oxo-pyrrolidin-1-yl)-benzyl]-3H-imidazol-4-ylmethyl}-benzonitrile
- 4-{3-[4-(3-Methyl-2-oxo-2-H-pyrazin-1-yl)-benzyl]-3-H-imidazol-4-ylmethyl}-benzonitrile
- 10 4-{3-[2-Methoxy-4-(2-oxo-2-H-pyridin-1-yl)-benzyl]-3-H-imidazol-4-ylmethyl}-benzonitrile
- 4-{1-[4-(5-Chloro-2-oxo-2H-pyridin-1-yl)-benzyl]-1H-pyrrol-2-ylmethyl}-benzonitrile
- 15 4-[1-(2-Oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-pyrrol-2-ylmethyl]-benzonitrile
- 4-[1-(5-Chloro-2-oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-pyrrol-2-ylmethyl]-benzonitrile
- 20 4-[3-(2-Oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl]benzonitrile
- 4-{3-[1-(3-Chloro-phenyl)-2-oxo-1,2-dihydropyridin-4-ylmethyl]-3H-imidazol-4-ylmethyl}benzonitrile
- 25

or a pharmaceutically acceptable salt, disulfide or optical isomer thereof.

Specific examples of a farnesyl-protein transferase inhibitor

- 30 is
 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone
 isopropyl ester (Compound A)



1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone;

5

(R)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)methyl]-2-piperazinone;

4-[1-(5-Chloro-2-oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-pyrrol-2-ylmethyl]-benzonitrile and

10

1-[N-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-N-(4-cyanobenzyl)amino]-4-(phenoxy)benzene;

15 or a pharmaceutically acceptable salt, disulfide or optical isomer thereof.

A particularly useful example of the instant method comprises administering an effective amount of a combination of

20

2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]-pentylloxy-3-phenylpropionyl-methionine sulfone isopropyl ester (Compound A).

25

Another particularly useful example of the instant method comprises administering an effective amount of a combination of vinblastine and a farnesyl-protein transferase inhibitor which is:

- 5 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone isopropyl ester (Compound A).

- 10 Another particularly useful example of the instant method comprises administering an effective amount of a combination of 5-fluorouracil and a farnesyl-protein transferase inhibitor which is:

- 15 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone isopropyl ester (Compound A).

- 20 Another particularly useful example of the instant method comprises administering an effective amount of a combination of colchicine and a farnesyl-protein transferase inhibitor which is:

- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone isopropyl ester (Compound A).

- 25 Another particularly useful example of the instant method comprises administering an effective amount of a combination of estramustine and a farnesyl-protein transferase inhibitor which is:

- 30 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone isopropyl ester (Compound A).

Another particularly useful example of the instant method comprises administering an effective amount of a combination of etoposide and a farnesyl-protein transferase inhibitor which is:

- 5 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-
3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone
isopropyl ester (Compound A).

- 10 Another particularly useful example of the instant method
comprises administering an effective amount of a combination of
doxorubicin and a farnesyl-protein transferase inhibitor which is:

- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-
3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone
15 isopropyl ester (Compound A).

- Another particularly useful example of the instant method
comprises administering an effective amount of a combination of cis-
platinum and a farnesyl-protein transferase inhibitor which is:

- 20 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-
3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone
isopropyl ester (Compound A).

- 25 Another particularly useful example of the instant method
comprises administering an effective amount of a combination of
bicalutamide and a farnesyl-protein transferase inhibitor which is:

- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-
30 3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone
isopropyl ester (Compound A).

Another particularly useful example of the instant method comprises administering an effective amount of a combination of epoithilone A and a farnesyl-protein transferase inhibitor which is:

- 5 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone isopropyl ester (Compound A).

- Another particularly useful example of the instant method
10 comprises administering an effective amount of a combination of epoithilone B and a farnesyl-protein transferase inhibitor which is:

- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone
15 isopropyl ester (Compound A).

- Another particularly useful example of the instant method comprises administering an effective amount of a combination of desoxyepoithilone A and a farnesyl-protein transferase inhibitor which
20 is:

- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone isopropyl ester (Compound A).
25

- Another particularly useful example of the instant method comprises administering an effective amount of a combination of desoxyepoithilone B and a farnesyl-protein transferase inhibitor which
30 is:

- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone isopropyl ester (Compound A).

A particularly useful example of the instant method comprises administering an effective amount of a combination of paclitaxel and a farnesyl-protein transferase inhibitor which is:

- 5 1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone;
or a pharmaceutically acceptable salt thereof.

- 10 Another particularly useful example of the instant method comprises administering an effective amount of a combination of vinblastine and a farnesyl-protein transferase inhibitor which is:

- 1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone;
15 or a pharmaceutically acceptable salt thereof.

- Another particularly useful example of the instant method comprises administering an effective amount of a combination of 5-fluorouracil and a farnesyl-protein transferase inhibitor which is:

- 20 1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone;
or a pharmaceutically acceptable salt thereof.

- 25 Another particularly useful example of the instant method comprises administering an effective amount of a combination of colchicine and a farnesyl-protein transferase inhibitor which is:

- 1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone;
30 or a pharmaceutically acceptable salt thereof.

- Another particularly useful example of the instant method comprises administering an effective amount of a combination of estramustine and a farnesyl-protein transferase inhibitor which is:

- 35

1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone;
or a pharmaceutically acceptable salt thereof.

5

Another particularly useful example of the instant method comprises administering an effective amount of a combination of etoposide and a farnesyl-protein transferase inhibitor which is:

- 10 1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone;
or a pharmaceutically acceptable salt thereof.

- 15 Another particularly useful example of the instant method comprises administering an effective amount of a combination of doxorubicin and a farnesyl-protein transferase inhibitor which is:

- 1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone;
20 or a pharmaceutically acceptable salt thereof.

- Another particularly useful example of the instant method comprises administering an effective amount of a combination of cis-platinum and a farnesyl-protein transferase inhibitor which is:

25

1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone;
or a pharmaceutically acceptable salt thereof.

- 30 Another particularly useful example of the instant method comprises administering an effective amount of a combination of bicalutamide and a farnesyl-protein transferase inhibitor which is:

- 1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone;
35

or a pharmaceutically acceptable salt thereof.

- Another particularly useful example of the instant method comprises administering an effective amount of a combination of
5 epothilone A and a farnesyl-protein transferase inhibitor which is:

1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone;

or a pharmaceutically acceptable salt thereof.

10

Another particularly useful example of the instant method comprises administering an effective amount of a combination of
epothilone B and a farnesyl-protein transferase inhibitor which is:

- 15 1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone;

or a pharmaceutically acceptable salt thereof.

- 20 Another particularly useful example of the instant method comprises administering an effective amount of a combination of desoxyepothilone A and a farnesyl-protein transferase inhibitor which is:

1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone;

25

or a pharmaceutically acceptable salt thereof.

- Another particularly useful example of the instant method comprises administering an effective amount of a combination of
30 desoxyepothilone B and a farnesyl-protein transferase inhibitor which is:

1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone;

or a pharmaceutically acceptable salt thereof.

- 5 A particularly useful example of the instant method comprises administering an effective amount of a combination of paclitaxel and a farnesyl-protein transferase inhibitor which is:

(R)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)methyl]-2-piperazinone;
or a pharmaceutically acceptable salt thereof.

10

Another particularly useful example of the instant method comprises administering an effective amount of a combination of vinblastine and a farnesyl-protein transferase inhibitor which is:

- 15 (R)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)methyl]-2-piperazinone;
or a pharmaceutically acceptable salt thereof.

- 20 Another particularly useful example of the instant method comprises administering an effective amount of a combination of 5-fluorouracil and a farnesyl-protein transferase inhibitor which is:

- (R)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)methyl]-2-piperazinone;
25 or a pharmaceutically acceptable salt thereof.

- Another particularly useful example of the instant method comprises administering an effective amount of a combination of colchicine and a farnesyl-protein transferase inhibitor which is:

30

(R)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)methyl]-2-piperazinone;
or a pharmaceutically acceptable salt thereof.

Another particularly useful example of the instant method comprises administering an effective amount of a combination of estramustine and a farnesyl-protein transferase inhibitor which is:

- 5 (R)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)methyl]-2-piperazinone;
or a pharmaceutically acceptable salt thereof.

- Another particularly useful example of the instant method
10 comprises administering an effective amount of a combination of etoposide and a farnesyl-protein transferase inhibitor which is:

- (R)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)methyl]-2-piperazinone;
15 or a pharmaceutically acceptable salt thereof.

- Another particularly useful example of the instant method comprises administering an effective amount of a combination of doxorubicin and a farnesyl-protein transferase inhibitor which is:
20

(R)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)methyl]-2-piperazinone;
or a pharmaceutically acceptable salt thereof.

- 25 Another particularly useful example of the instant method comprises administering an effective amount of a combination of cis-platinum and a farnesyl-protein transferase inhibitor which is:

- (R)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)methyl]-2-piperazinone;
30 or a pharmaceutically acceptable salt thereof.

- Another particularly useful example of the instant method comprises administering an effective amount of a combination of
35 bicalutamide and a farnesyl-protein transferase inhibitor which is:

(R)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)methyl]-2-piperazinone;
or a pharmaceutically acceptable salt thereof.

5

Another particularly useful example of the instant method comprises administering an effective amount of a combination of epothilone A and a farnesyl-protein transferase inhibitor which is:

- 10 (R)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)methyl]-2-piperazinone;
or a pharmaceutically acceptable salt thereof.

- 15 Another particularly useful example of the instant method comprises administering an effective amount of a combination of epothilone B and a farnesyl-protein transferase inhibitor which is:

- (R)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)methyl]-2-piperazinone;
20 or a pharmaceutically acceptable salt thereof.

- Another particularly useful example of the instant method comprises administering an effective amount of a combination of desoxyepothilone A and a farnesyl-protein transferase inhibitor which
25 is:

- (R)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)methyl]-2-piperazinone;
or a pharmaceutically acceptable salt thereof.
30

Another particularly useful example of the instant method comprises administering an effective amount of a combination of desoxyepothilone B and a farnesyl-protein transferase inhibitor which is:

(R)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolymethyl]-5-[2-(ethanesulfonyl)methyl]-2-piperazinone;
or a pharmaceutically acceptable salt thereof.

5

Another particularly useful example of the instant method comprises administering an effective amount of a combination of paclitaxel and a farnesyl-protein transferase inhibitor which is:

- 10 4-[1-(5-Chloro-2-oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-pyrrol-2-ylmethyl]-benzonitrile;
or a pharmaceutically acceptable salt thereof.

- 15 Another particularly useful example of the instant method comprises administering an effective amount of a combination of vinblastine and a farnesyl-protein transferase inhibitor which is:

- 4-[1-(5-Chloro-2-oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-pyrrol-2-ylmethyl]-benzonitrile;
20 or a pharmaceutically acceptable salt thereof.

- Another particularly useful example of the instant method comprises administering an effective amount of a combination of 5-fluorouracil and a farnesyl-protein transferase inhibitor which is:

25

4-[1-(5-Chloro-2-oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-pyrrol-2-ylmethyl]-benzonitrile;
or a pharmaceutically acceptable salt thereof.

- 30 Another particularly useful example of the instant method comprises administering an effective amount of a combination of colchicine and a farnesyl-protein transferase inhibitor which is:

- 4-[1-(5-Chloro-2-oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-pyrrol-2-ylmethyl]-benzonitrile;
35

or a pharmaceutically acceptable salt thereof.

- Another particularly useful example of the instant method comprises administering an effective amount of a combination of estramustine and a farnesyl-protein transferase inhibitor which is:

4-[1-(5-Chloro-2-oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-pyrrol-2-ylmethyl]-benzonitrile;
or a pharmaceutically acceptable salt thereof.

10

Another particularly useful example of the instant method comprises administering an effective amount of a combination of etoposide and a farnesyl-protein transferase inhibitor which is:

- 15 4-[1-(5-Chloro-2-oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-pyrrol-2-ylmethyl]-benzonitrile;
or a pharmaceutically acceptable salt thereof.

- Another particularly useful example of the instant method comprises administering an effective amount of a combination of doxorubicin and a farnesyl-protein transferase inhibitor which is:

- 20 4-[1-(5-Chloro-2-oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-pyrrol-2-ylmethyl]-benzonitrile;
25 or a pharmaceutically acceptable salt thereof.

- Another particularly useful example of the instant method comprises administering an effective amount of a combination of cis-platinum and a farnesyl-protein transferase inhibitor which is:

30

4-[1-(5-Chloro-2-oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-pyrrol-2-ylmethyl]-benzonitrile;
or a pharmaceutically acceptable salt thereof.

Another particularly useful example of the instant method comprises administering an effective amount of a combination of bicalutamide and a farnesyl-protein transferase inhibitor which is:

- 5 4-[1-(5-Chloro-2-oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-pyrrol-2-ylmethyl]-benzonitrile;
or a pharmaceutically acceptable salt thereof.

- 10 Another particularly useful example of the instant method comprises administering an effective amount of a combination of epothilone A and a farnesyl-protein transferase inhibitor which is:

- 4-[1-(5-Chloro-2-oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-pyrrol-2-ylmethyl]-benzonitrile;
15 or a pharmaceutically acceptable salt thereof.

- Another particularly useful example of the instant method comprises administering an effective amount of a combination of epothilone B and a farnesyl-protein transferase inhibitor which is:

- 20 4-[1-(5-Chloro-2-oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-pyrrol-2-ylmethyl]-benzonitrile;
or a pharmaceutically acceptable salt thereof.

- 25 Another particularly useful example of the instant method comprises administering an effective amount of a combination of desoxyepothilone A and a farnesyl-protein transferase inhibitor which is:

- 30 4-[1-(5-Chloro-2-oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-pyrrol-2-ylmethyl]-benzonitrile;
or a pharmaceutically acceptable salt thereof.

Another particularly useful example of the instant method comprises administering an effective amount of a combination of desoxyepothilone B and a farnesyl-protein transferase inhibitor which is:

5

4-[1-(5-Chloro-2-oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-pyrrol-2-ylmethyl]-benzonitrile;
or a pharmaceutically acceptable salt thereof.

10

Another particularly useful example of the instant method comprises administering an effective amount of a combination of paclitaxel and a farnesyl-protein transferase inhibitor which is:

15

1-[N-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-N-(4-cyanobenzyl)amino]-4-(phenoxy)benzene;
or a pharmaceutically acceptable salt thereof.

20

Another particularly useful example of the instant method comprises administering an effective amount of a combination of vinblastine and a farnesyl-protein transferase inhibitor which is:

25

1-[N-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-N-(4-cyanobenzyl)amino]-4-(phenoxy)benzene;
or a pharmaceutically acceptable salt thereof.

30

Another particularly useful example of the instant method comprises administering an effective amount of a combination of 5-fluorouracil and a farnesyl-protein transferase inhibitor which is:

30

1-[N-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-N-(4-cyanobenzyl)amino]-4-(phenoxy)benzene;
or a pharmaceutically acceptable salt thereof.

Another particularly useful example of the instant method comprises administering an effective amount of a combination of colchicine and a farnesyl-protein transferase inhibitor which is:

- 5 1-[N-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-N-(4-cyanobenzyl)amino]-4-(phenoxy)benzene;
or a pharmaceutically acceptable salt thereof.

- Another particularly useful example of the instant method
10 comprises administering an effective amount of a combination of estramustine and a farnesyl-protein transferase inhibitor which is:

- 1-[N-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-N-(4-
cyanobenzyl)amino]-4-(phenoxy)benzene;
15 or a pharmaceutically acceptable salt thereof.

- Another particularly useful example of the instant method
comprises administering an effective amount of a combination of
etoposide and a farnesyl-protein transferase inhibitor which is:

- 20 1-[N-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-N-(4-cyanobenzyl)amino]-4-(phenoxy)benzene;
or a pharmaceutically acceptable salt thereof.

- 25 Another particularly useful example of the instant method
comprises administering an effective amount of a combination of
doxorubicin and a farnesyl-protein transferase inhibitor which is:

- 1-[N-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-N-(4-
30 cyanobenzyl)amino]-4-(phenoxy)benzene;
or a pharmaceutically acceptable salt thereof.

- Another particularly useful example of the instant method
comprises administering an effective amount of a combination of cis-
35 platinum and a farnesyl-protein transferase inhibitor which is:

1-[N-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-N-(4-cyanobenzyl)amino]-4-(phenoxy)benzene;
or a pharmaceutically acceptable salt thereof.

5

Another particularly useful example of the instant method comprises administering an effective amount of a combination of bicalutamide and a farnesyl-protein transferase inhibitor which is:

- 10 1-[N-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-N-(4-cyanobenzyl)amino]-4-(phenoxy)benzene;
or a pharmaceutically acceptable salt thereof.

- 15 Another particularly useful example of the instant method comprises administering an effective amount of a combination of epothilone A and a farnesyl-protein transferase inhibitor which is:

- 20 1-[N-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-N-(4-cyanobenzyl)amino]-4-(phenoxy)benzene;
or a pharmaceutically acceptable salt thereof.

- 25 Another particularly useful example of the instant method comprises administering an effective amount of a combination of epothilone B and a farnesyl-protein transferase inhibitor which is:

- 1-[N-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-N-(4-cyanobenzyl)amino]-4-(phenoxy)benzene;
or a pharmaceutically acceptable salt thereof.

- 30 Another particularly useful example of the instant method comprises administering an effective amount of a combination of desoxyepothilone A and a farnesyl-protein transferase inhibitor which is:

1-[N-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-N-(4-cyanobenzyl)amino]-4-(phenoxy)benzene;
or a pharmaceutically acceptable salt thereof.

- 5 Another particularly useful example of the instant method comprises administering an effective amount of a combination of desoxyepothilone B and a farnesyl-protein transferase inhibitor which is:

- 10 1-[N-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-N-(4-cyanobenzyl)amino]-4-(phenoxy)benzene;
or a pharmaceutically acceptable salt thereof.

- 15 Compounds which are described as inhibitors of farnesyl-protein transferase and may therefore useful in the present invention, and methods of synthesis thereof, can be found in the following patents, pending applications and publications, which are herein incorporated by reference:

- WO 95/32987 published on 7 December 1995;
20 U. S. Pat. No. 5,420,245;
U. S. Pat. No. 5,523,430;
U. S. Pat. No. 5,532,359;
U. S. Pat. No. 5,510,510;
U. S. Pat. No. 5,589,485;
25 U. S. Pat. No. 5,602,098;
European Pat. Publ. 0 618 221;
European Pat. Publ. 0 675 112;
European Pat. Publ. 0 604 181;
European Pat. Publ. 0 696 593;
30 WO 94/19357;
WO 95/08542 ;
WO 95/11917;
WO 95/12612;
WO 95/12572;

- WO 95/10514 and U.S. Pat. No. 5,661,152;
WO 95/10515;
WO 95/10516;
WO 95/24612;
5 WO 95/34535;
WO 95/25086;
WO 96/05529;
WO 96/06138;
WO 96/06193;
10 WO 96/16443;
WO 96/21701;
WO 96/21456;
WO 96/22278;
WO 96/24611;
15 WO 96/24612;
WO 96/05168;
WO 96/05169;
WO 96/00736 and U.S. Pat. No. 5,571,792 granted on November 5,
1996;
20 WO 96/17861;
WO 96/33159;
WO 96/34850;
WO 96/34851;
WO 96/30017;
25 WO 96/30018;
WO 96/30362;
WO 96/30363;
WO 96/31111;
WO 96/31477;
30 WO 96/31478;
WO 96/31501;
WO 97/00252;
WO 97/03047;
WO 97/03050;

- WO 97/04785;
WO 97/02920;
WO 97/17070;
WO 97/23478;
5 WO 97/26246;
WO 97/30053;
WO 97/44350;
WO 98/02436; and
U. S. Pat. No. 5,532,359 granted on July 2, 1996.

10

Compounds which are inhibitors of farnesyl-protein transferase and are therefore useful in the present invention, and methods of synthesis thereof, can be found in the following patents, pending applications and publications, which are herein incorporated by reference:

15

U. S. Pat. No. 5,238,922 granted on August 24, 1993;

U. S. Pat. No. 5,340,828 granted on August 23, 1994;

20

U. S. Pat. No. 5,480,893 granted on January 2, 1996;

U. S. Pat. No. 5,352,705 granted on October 4, 1994;

25 U. S. Pat. No. 5,504,115 granted on April 2, 1996;

U. S. Pat. No. 5,536,750 granted on July 16, 1996;

U. S. Pat. No. 5,504,212 granted on April 2, 1996;

30

U. S. Pat. No. 5,439,918 granted on August 8, 1995;

U. S. Pat. No. 5,686,472 granted on November 11, 1997;

35 U. S. Pat. No. 5,736,539 granted on April 4, 1998;

- U. S. Pat. No. 5,576,293 granted on November 19, 1996;
- U. S. Pat. No. 5,468,733 granted on November 21, 1995;
- 5 WO 96/06609 (March 3, 1996) and USSN 08/298,478 filed on August 24, 1994;
- U. S. Pat. No. 5,585,359 granted on December 17, 1996
- 10 U. S. Pat. No. 5,523,456 granted on June 4, 1996;
- U. S. Pat. No. 5,661,161 granted on August 26, 1997;
- U. S. Pat. No. 5,571,835 granted on November 5, 1996;
- 15 U. S. Pat. No. 5,491,164 granted on February 13, 1996;
- U. S. Pat. No. 5,652,257 granted on July 29, 1997;
- 20 U. S. Pat. No. 5,631,280 granted on May 20, 1997;
- U. S. Pat. No. 5,578,629 granted on November 26, 1996;
- U. S. Pat. No. 5,627,202 granted on May 6, 1997;
- 25 WO 96/30343 (October 3, 1996); USSN 08/412,829 filed on March 29, 1995; and USSN 08/470,690 filed on June 6, 1995; and USSN 08/600,728 filed on February 28, 1996;
- 30 U. S. Pat. No. 5,624,936 granted on April 29, 1997;
- U. S. Pat. No. 5,534,537 granted on July 9, 1996;
- U. S. Pat. No. 5,710,171 granted on April 29, 1997;
- 35

WO 96/39137 (December 12, 1996); USSN 08/468,160 filed on June 6, 1995; USSN 08/652,055 filed on May 23, 1996; USSN 08/960,248 filed October 29, 1997;

- 5 U. S. Pat. No. 5,703,241 granted on December 30, 1997;

WO 97/18813; USSN 08/749,254 filed on November 15, 1996;

- 10 WO 97/27854 (August 7, 1997); USSN 60/010,799 filed on January 30, 1996; USSN 08/786,520 filed on January 21, 1997; USSN 09/015,823 filed on January 29, 1998;

- 15 WO 97/27752 (August 7, 1997); USSN 60/010,860 filed on January 30, 1996; USSN 08/784,556 filed on January 21, 1997; USSN 09/030,223 filed on February 25, 1998;

- 20 WO 97/27853 (August 7, 1997); USSN 60/011,081 filed on January 30, 1996; USSN 08/786,519 filed on January 21, 1997; USSN 09/_____ filed on March 20, 1998;

WO 97/27852 (August 7, 1997); USSN 60/010,798 filed on January 30, 1996; USSN 08/786,516 filed on January 21, 1997;

- 25 WO 97/36888 (October 9, 1997); USSN 60/014,587 filed on April 3, 1996; USSN 08/823,919 filed on March 25, 1997;

WO 97/36889 (October 9, 1997); USSN 60/014,589 filed on April 3, 1996; USSN 08/823,923 filed on March 25, 1997;

- 30 WO 97/36876 (October 9, 1997); USSN 60/014,592 filed on April 3, 1996; USSN 08/834,671 filed on April 1, 1997;

WO 97/36593 (October 9, 1997); USSN 60/014,593 filed on April 3, 1996; USSN 08/827,485, filed on March 27, 1997;

WO 97/36879 (October 9, 1997); USSN 60/014,594 filed on April 3, 1996; USSN 08/823,920 filed on March 25, 1997;

- 5 WO 97/36583 (October 9, 1997); USSN 60/014,668 filed on April 3, 1996; USSN 08/824,588 filed on March 26, 1997;

WO 97/36592 (October 9, 1997); USSN 60/014,775 filed on April 3, 1996; USSN 08/826,292 filed on March 27, 1997;

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WO 97/36584 (October 9, 1997); USSN 60/014,776 filed on April 3, 1996; USSN 08/824,427 filed on March 26, 1997;

- 15 USSN 60/014,777 filed on April 3, 1996; USSN 08/826,317 filed on March 27, 1997;

WO 97/38665 (October 23, 1997); USSN 60/014,791 filed on April 3, 1996; USSN 08/831,308 filed on April 1, 1997;

- 20 WO 97/36591 (October 9, 1997); USSN 60/014,792 filed on April 3, 1996; USSN 08/827,482, filed on March 27, 1997;

WO 97/36605 (October 9, 1997); USSN 60/014,793 filed on April 3, 1996; USSN 08/823,934 filed on March 25, 1997;

25

WO 97/37877 (October 9, 1997); USSN 60/014,794 filed on April 3, 1996; USSN 08/834,675 filed on April 1, 1997;

- 30 WO 97/37900 (October 9, 1997); USSN 60/014,798 filed on April 3, 1996; USSN 08/823,929 filed on March 25, 1997;

WO 97/36891 (October 9, 1997); USSN 60/014,774 filed on April 3, 1996; USSN 08/826,291 filed on March 27, 1997;

- WO 97/36886 (October 9, 1997); USSN 60/022,332 filed on July 24, 1996; USSN 08/823,919, filed on March 27, 1997;
- 5 WO 97/36881 (October 9, 1997); USSN 60/022,340 filed on July 24, 1996; USSN 08/827,486, filed on March 27, 1997;
- WO 97/36585 (October 9, 1997); USSN 60/022,341 filed on July 24, 1996; USSN 08/826,251 filed on March 27, 1997;
- 10 WO 97/36898 (October 9, 1997); USSN 60/022,342 filed on July 24, 1996; USSN 08/825,293 filed on March 27, 1997;
- WO 97/36897 (October 9, 1997); USSN 60/022,558 filed on July 24, 1996; USSN 08/827,476, filed on March 27, 1997;
- 15 WO 97/36874 (October 9, 1997);
- WO 97/36585 (October 9, 1997); USSN 60/022,586 filed on July 24, 1996; USSN 08/827,484, filed on March 27, 1997;
- 20 WO 97/36890 (October 9, 1997); USSN 60/022,587 filed on July 24, 1996; USSN 08/831,105 filed on April 1, 1997;
- WO 97/36901 (October 9, 1997); USSN 60/022,647 filed on July 24, 1996; USSN 08/827,483, filed on March 27, 1997;
- 25 USSN 60/032,126 filed on December 5, 1996; USSN 08/985,732, filed on December 4, 1997;
- 30 USSN 60/032,428 filed on December 5, 1996; USSN 08/985,124, filed on December 4, 1997;
- USSN 60/032,578 filed on December 5, 1996; USSN 08/985,337, filed on December 4, 1997;

USSN 60/032,579 filed on December 5, 1996; USSN 08/985,320, filed on December 5, 1997;

- 5 USSN 60/033,990, filed on December 30, 1996; USSN 08/995,744, filed on December 22, 1997; and

USSN 60/033,991, filed on December 30, 1996; USSN 08/985,124, filed on December 5, 1997.

10

All patents, publications and pending patent applications identified are hereby incorporated by reference.

With respect to the compounds of formulas II-a through II-n the following definitions apply:

- 15 The term "alkyl" refers to a monovalent alkane (hydrocarbon) derived radical containing from 1 to 15 carbon atoms unless otherwise defined. It may be straight, branched or cyclic. Preferred straight or branched alkyl groups include methyl, ethyl, propyl, isopropyl, butyl and t-butyl. Preferred cycloalkyl groups
20 include cyclopentyl and cyclohexyl.

When substituted alkyl is present, this refers to a straight, branched or cyclic alkyl group as defined above, substituted with 1-3 groups as defined with respect to each variable.

- 25 Heteroalkyl refers to an alkyl group having from 2-15 carbon atoms, and interrupted by from 1-4 heteroatoms selected from O, S and N.

- The term "alkenyl" refers to a hydrocarbon radical straight, branched or cyclic containing from 2 to 15 carbon atoms and at least one carbon to carbon double bond. Preferably one
30 carbon to carbon double bond is present, and up to four non-aromatic (non-resonating) carbon-carbon double bonds may be present. Examples of alkenyl groups include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, 1-propenyl, 2-butenyl, 2-methyl-2-

- butenyl, isoprenyl, farnesyl, geranyl, geranylgeranyl and the like. Preferred alkenyl groups include ethenyl, propenyl, butenyl and cyclohexenyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkenyl group may contain double bonds and may be substituted when a substituted alkenyl group is provided.

- The term "alkynyl" refers to a hydrocarbon radical straight, branched or cyclic, containing from 2 to 15 carbon atoms and at least one carbon to carbon triple bond. Up to three carbon-carbon triple bonds may be present. Preferred alkynyl groups include ethynyl, propynyl and butynyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkynyl group may contain triple bonds and may be substituted when a substituted alkynyl group is provided.

- Aryl refers to aromatic rings e.g., phenyl, substituted phenyl and like groups as well as rings which are fused, e.g., naphthyl and the like. Aryl thus contains at least one ring having at least 6 atoms, with up to two such rings being present, containing up to 10 atoms therein, with alternating (resonating) double bonds between adjacent carbon atoms. The preferred aryl groups are phenyl and naphthyl. Aryl groups may likewise be substituted as defined below. Preferred substituted aryls include phenyl and naphthyl substituted with one or two groups. With regard to the farnesyl transferase inhibitors, "aryl" is intended to include any stable monocyclic, bicyclic or tricyclic carbon ring(s) of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of aryl groups include phenyl, naphthyl, anthracenyl, biphenyl, tetrahydronaphthyl, indanyl, phenanthrenyl and the like.

- The term "heteroaryl" refers to a monocyclic aromatic hydrocarbon group having 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing at least one heteroatom, O, S or N, in which a carbon or nitrogen atom is the point of attachment, and in which one additional carbon atom is optionally replaced by a heteroatom selected from O or S, and in which from

1 to 3 additional carbon atoms are optionally replaced by nitrogen heteroatoms. The heteroaryl group is optionally substituted with up to three groups.

Heteroaryl thus includes aromatic and partially aromatic groups which contain one or more heteroatoms. Examples of this type are thiophene, purine, imidazopyridine, pyridine, oxazole, thiazole, oxazine, pyrazole, tetrazole, imidazole, pyridine, pyrimidine, pyrazine and triazine. Examples of partially aromatic groups are tetrahydro-imidazo[4,5-c]pyridine, phthalidyl and saccharinyl, as defined below.

With regard to the farnesyl transferase inhibitors, the term heterocycle or heterocyclic, as used herein, represents a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic or stable 11-15 membered tricyclic heterocycle ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic elements include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnoliny, dihydrobenzofuryl, dihydro-benzothienyl, dihydrobenzothiopyranyl, dihydrobenzothio-pyranyl sulfone, furyl, imidazolidinyl, imidazoliny, imidazolyl, indoliny, indolyl, isochromanyl, isoindoliny, isoquinoliny, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholiny, naphthyrinyl, oxadiazolyl, 2-oxoazepinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyridyl N-oxide, pyridonyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazoliny, quinoliny, quinoliny N-oxide, quinoxaliny, tetrahydrofuryl, tetrahydroisoquinoliny, tetrahydro-quinoliny, thiamorpholiny, thiamorpholiny sulfoxide, thiazolyl, thiazoliny, thienofuryl, thienothienyl, and thienyl.

Preferably, heterocycle is selected from imidazolyl, 2-oxopyrrolidinyl, piperidyl, pyridyl and pyrrolidinyl.

- With regard to the farnesyl transferase inhibitors, the terms "substituted aryl", "substituted heterocycle" and "substituted cycloalkyl" are intended to include the cyclic group which is substituted with 1 or 2 substituents selected from the group which includes but is not limited to F, Cl, Br, CF₃, NH₂, N(C₁-C₆ alkyl)₂, NO₂, CN, (C₁-C₆ alkyl)O-, -OH, (C₁-C₆ alkyl)S(O)_m, (C₁-C₆ alkyl)C(O)NH-, H₂N-C(NH)-, (C₁-C₆ alkyl)C(O)-, (C₁-C₆ alkyl)OC(O)-, N₃, (C₁-C₆ alkyl)OC(O)NH- and C₁-C₂₀ alkyl.

In the present method, amino acids which are disclosed are identified both by conventional 3 letter and single letter abbreviations as indicated below:

15	Alanine	Ala	A
	Arginine	Arg	R
	Asparagine	Asn	N
	Aspartic acid	Asp	D
	Asparagine or		
20	Aspartic acid	Asx	B
	Cysteine	Cys	C
	Glutamine	Gln	Q
	Glutamic acid	Glu	E
	Glutamine or		
25	Glutamic acid	Glx	Z
	Glycine	Gly	G
	Histidine	His	H
	Isoleucine	Ile	I
	Leucine	Leu	L
30	Lysine	Lys	K
	Methionine	Met	M
	Phenylalanine	Phe	F
	Proline	Pro	P
	Serine	Ser	S
35	Threonine	Thr	T

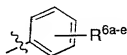
Tryptophan	Trp	W
Tyrosine	Tyr	Y
Valine	Val	V

5

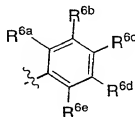
The compounds used in the present method may have asymmetric centers and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers, including optical isomers, being included in the present invention. Unless otherwise specified, named amino acids are understood to have the natural "L" stereoconfiguration.

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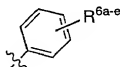
With respect to the farnesyl-protein transferase inhibitors of the formulas II-d and II-f, the substituent illustrated by the structure



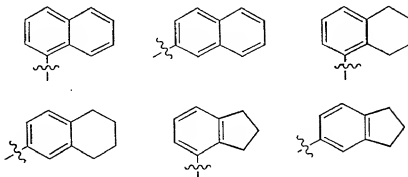
15 is a simplified representation of a phenyl ring having five (5) substituents (hydrogens and/or non-hydrogens) and may also be represented by the structure:



20 With respect to the farnesyl-protein transferase inhibitors of the formulas II-d and II-f, the moiety described as



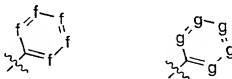
where any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH-, -(CH₂)₄- and -(CH₂)₄- includes the following structures:



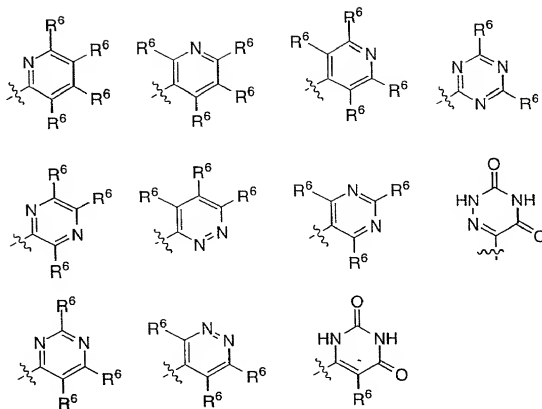
- 5 It is understood that such fused ring moieties may be further substituted by the remaining R^{6a}, R^{6b}, R^{6c}, R^{6d} and/or R^{6e} as defined hereinabove.

With respect to the farnesyl-protein transferase inhibitors of the formulas II-e and II-g, the moieties designated by the following

- 10 structures:



represent an aromatic 6-membered heterocyclic ring and includes the following ring systems:

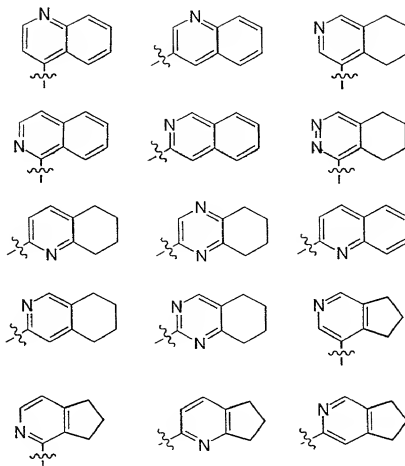


wherein R^6 is as defined hereinabove.

- With respect to the farnesyl-protein transferase inhibitors of the formulas II-e and II-g, the moieties designated by the following structures:



where any two of R^6 on adjacent carbon atoms are combined to form a diradical selected from $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$, $-\text{CH}=\text{CH}-\text{CH}-$, $-(\text{CH}_2)_4-$ and $-(\text{CH}_2)_4-$ include, but are not limited to the following structures:

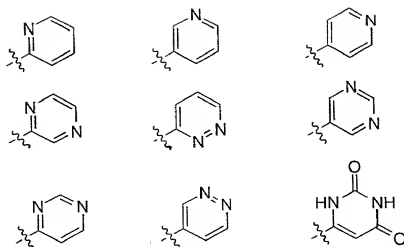


It is understood that such fused ring moieties may be further substituted by the remaining R^6 s as defined hereinabove.

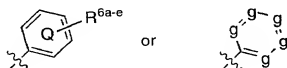
- With respect to the farnesyl-protein transferase inhibitors
 5 of the formulas II-f and II-g, the moiety designated by the following structure:



represents an aromatic 6-membered heterocyclic ring and includes the following ring systems:



wherein it is understood that one of the ring carbon atoms is substituted with

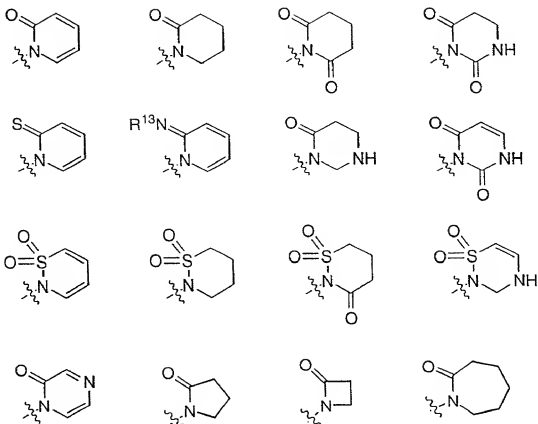


5 respectively.

With respect to the farnesyl-protein transferase inhibitors of the formula II-m, the substituent illustrated by the structure:

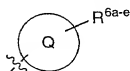


10 represents a 4, 5, 6 or 7 membered heterocyclic ring which comprises a nitrogen atom through which Q is attached to Y and 0-2 additional heteroatoms selected from N, S and O, and which also comprises a carbonyl, thiocarbonyl, $-C(=NR^{13})-$ or sulfonyl moiety adjacent to the nitrogen atom attached to Y and includes the following ring systems:

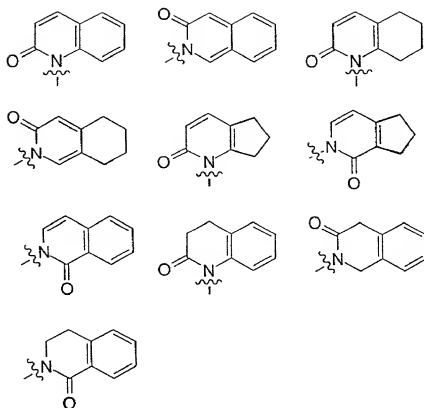


It is understood that such rings may be substituted by R^{6a}, R^{6b}, R^{6c}, R^{6d} and/or R^{6e} as defined hereinabove.

With respect to the farnesyl-protein transferase inhibitors
 5 of the formula II-m, the moiety described as



where any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon
 atoms are combined to form a diradical selected from -CH=CH-CH=CH,
 -CH=CH-CH-, -(CH₂)₄- and -(CH₂)₄- includes, but is not limited to,
 10 the following structures:

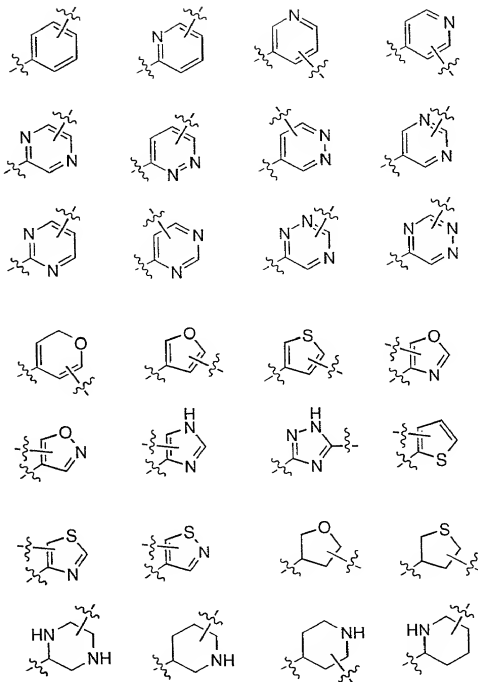


It is understood that such fused ring moieties may be further substituted by the remaining R6a, R6b, R6c, R6d and/or R6e as defined hereinabove.

- 5 With respect to the farnesyl-protein transferase inhibitors of the formula II-m, the substituent illustrated by the structure:



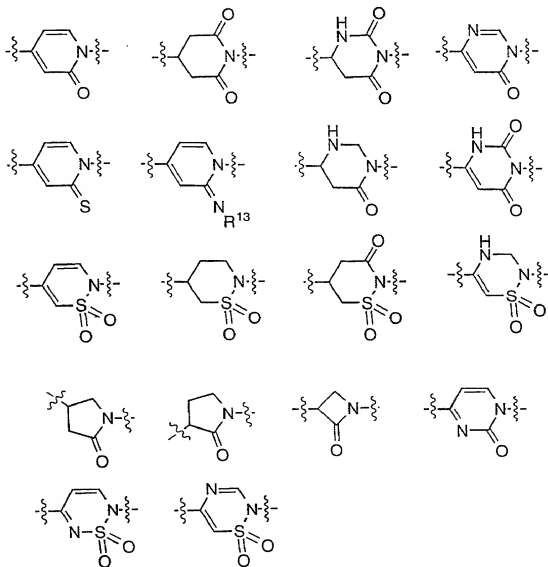
- 10 represents a 5, 6 or 7 membered carbocyclic ring wherein from 0 to 3 carbon atoms are replaced by a heteroatom selected from N, S and O, and wherein Y is attached to Q through a carbon atom and includes the following ring systems:



With respect to the farnesyl-protein transferase inhibitors of the formula II-n, the substituent illustrated by the structure:



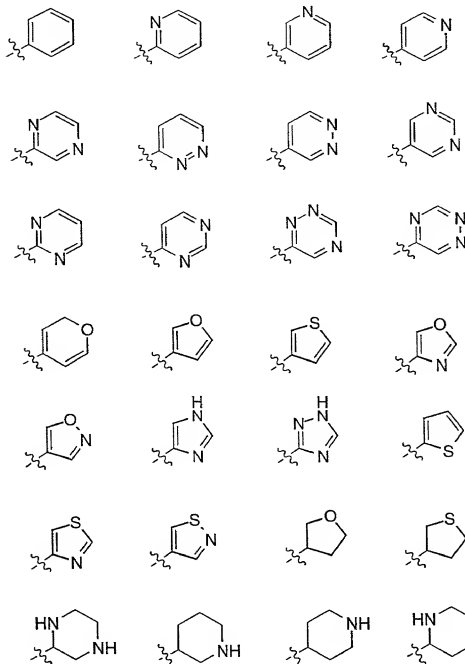
- represents a 4, 5, 6 or 7 membered heterocyclic ring which comprises a nitrogen atom through which Q is attached to Y and 0-2 additional heteroatoms selected from N, S and O, and which also comprises a carbonyl, thiocarbonyl, $-C(=NR^{13})-$ or sulfonyl moiety adjacent to the nitrogen atom attached to Y and includes the following ring systems:



With respect to the farnesyl-protein transferase inhibitors of the formula II-n, the substituent illustrated by the structure:



represents a 5-, 6- or 7-membered carbocyclic ring wherein from 0 to 3 carbon atoms are replaced by a heteroatom selected from N, S and O, and wherein Y is attached to Q through a carbon atom and includes the following ring systems:



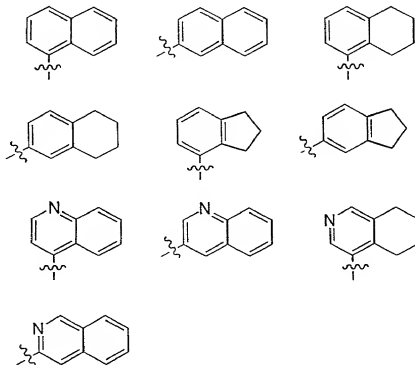
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With respect to the farnesyl-protein transferase inhibitors of the formula II-n, the moiety described as



where any two of R^{6a} , R^{6b} , R^{6c} , R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$, $-\text{CH}=\text{CH}-\text{CH}-$, $-(\text{CH}_2)_4-$ and $-(\text{CH}_2)_4-$ includes, but is not limited to,

5 the following structures:



It is understood that such fused ring moieties may be further substituted by the remaining R^{6a} , R^{6b} , R^{6c} , R^{6d} and/or R^{6e} as defined hereinabove.

10

When R^2 and R^3 are combined to form $-(\text{CH}_2)_u-$, cyclic moieties are formed. Examples of such cyclic moieties include, but are not limited to:



In addition, such cyclic moieties may optionally include a heteroatom(s). Examples of such heteroatom-containing cyclic moieties include, but are not limited to:

COR¹⁰

5

When R⁶ and R⁷, R⁷ and R^{7a}, or are combined to form - (CH₂)_u -, cyclic moieties are formed. Examples of such cyclic moieties include, but are not limited to:



10

The pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed, e.g., from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic,

15

sulfuric, sulfamic, phosphoric, nitric and the like: and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenyl-acetic, glutamic, benzoic, salicylic, sulfanilic,

2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

It is intended that the definition of any substituent or variable (e.g., R¹⁰, Z, n, etc.) at a particular location in a molecule be independent of its definitions elsewhere in that molecule. Thus, -N(R¹⁰)₂ represents -NHH, -NHCH₃, -NHC₂H₅, etc. It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art as well as those methods set forth below.

The pharmaceutically acceptable salts of the compounds of this invention can be synthesized from the compounds of this invention which contain a basic moiety by conventional chemical methods.

Generally, the salts are prepared by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents.

The compounds of formula (II-h) can be synthesized from their constituent amino acids by conventional peptide synthesis techniques, and the additional methods described below. Standard methods of peptide synthesis are disclosed, for example, in the following works: Schroeder *et al.*, "*The Peptides*", Vol. I, Academic Press 1965, or Bodanszky *et al.*, "*Peptide Synthesis*", Interscience Publishers, 1966, or McOmie (ed.) "*Protective Groups in Organic Chemistry*", Plenum Press, 1973, or Barany *et al.*, "*The Peptides: Analysis, Synthesis, Biology*" 2, Chapter 1, Academic Press, 1980, or Stewart *et al.*, "*Solid Phase Peptide Synthesis*", Second Edition, Pierce Chemical Company, 1984. Also useful in exemplifying syntheses of specific unnatural amino acid residues are European Pat. Appl. No. 0 350 163 A2 (particularly page 51-52) and J. E. Baldwin *et al. Tetrahedron*, 50:5049-5066 (1994). With regards to the synthesis of instant compounds containing a (β-acetyl-amino)alanine residue at the C-terminus, use of the commercially

available N α -Z-L-2,3-diaminopropionic acid (Fluka) as a starting material is preferred.

Abbreviations used in the description of the chemistry and in the Examples that follow are:

- | | | |
|----|-------------------|---|
| 5 | Ac ₂ O | Acetic anhydride; |
| | Boc | t-Butoxycarbonyl; |
| | DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene; |
| | DMAP | 4-Dimethylaminopyridine; |
| 10 | DME | 1,2-Dimethoxyethane; |
| | DMF | Dimethylformamide; |
| | EDC | 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide-hydrochloride; |
| | HOBT | 1-Hydroxybenzotriazole hydrate; |
| 15 | Et ₃ N | Triethylamine; |
| | EtOAc | Ethyl acetate; |
| | FAB | Fast atom bombardment; |
| | HOObt | 3-Hydroxy-1,2,2-benzotriazin-4(3H)-one; |
| | HPLC | High-performance liquid chromatography; |
| 20 | MCPBA | m-Chloroperoxybenzoic acid; |
| | MsCl | Methanesulfonyl chloride; |
| | NaHMDS | Sodium bis(trimethylsilyl)amide; |
| | Py | Pyridine; |
| | TFA | Trifluoroacetic acid; |
| 25 | THF | Tetrahydrofuran. |

- The compounds are useful in various pharmaceutically acceptable salt forms. The term "pharmaceutically acceptable salt" refers to those salt forms which would be apparent to the pharmaceutical chemist. i.e., those which are substantially non-toxic and which provide the desired pharmacokinetic properties, palatability, absorption, distribution, metabolism or excretion. Other factors, more practical in nature, which are also important in the selection, are cost of the raw materials, ease of crystallization, yield, stability, hygroscopicity and flowability of the resulting bulk drug. Conveniently, pharmaceutical

compositions may be prepared from the active ingredients in combination with pharmaceutically acceptable carriers.

Pharmaceutically acceptable salts include conventional non-toxic salts or quarternary ammonium salts formed, e.g., from non-toxic inorganic or organic acids. Non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized by conventional chemical methods. Generally, the salts are prepared by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base, in a suitable solvent or solvent combination.

The farnesyl transferase inhibitors of formula (II-a) through (II-c) can be synthesized in accordance with Schemes 1-22, in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures. Substituents R, R^a and R^b, as shown in the Schemes, represent the substituents R², R³, R⁴, and R⁵; however their point of attachment to the ring is illustrative only and is not meant to be limiting.

These reactions may be employed in a linear sequence to provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the alkylation reactions described in the Schemes.

Synopsis of Schemes 1-22:

The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures, for

- the most part. In Scheme 1, for example, the synthesis of 2-alkyl substituted piperazines is outlined, and is essentially that described by J. S. Kiely and S. R. Priebe in Organic Preparations and Proceedings Int., **1990**, 22, 761-768. Boc-protected amino acids I, available commercially or by procedures known to those skilled in the art, can be coupled to N-benzyl amino acid esters using a variety of dehydrating agents such as DCC (dicyclohexylcarbodiimide) or EDC·HCl (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride) in a solvent such as methylene chloride, chloroform, dichloroethane, or in dimethylformamide.
- 10 The product II is then deprotected with acid, for example hydrogen chloride in chloroform or ethyl acetate, or trifluoroacetic acid in methylene chloride, and cyclized under weakly basic conditions to give the diketopiperazine III. Reduction of III with lithium aluminum hydride in refluxing ether gives the piperazine IV, which is protected as the Boc derivative V. The N-benzyl group can be cleaved under standard conditions of hydrogenation, e.g., 10% palladium on carbon at 60 psi hydrogen on a Parr apparatus for 24-48 h. The product VI can be treated with an acid chloride, or a carboxylic acid under standard dehydrating conditions to furnish the carboxamides VII; a final acid
- 20 deprotection as previously described gives the intermediate VIII (Scheme 2). The intermediate VIII can be reductively alkylated with a variety of aldehydes, such as IX. The aldehydes can be prepared by standard procedures, such as that described by O. P. Goel, U. Krolls, M. Stier and S. Kesten in Organic Syntheses, **1988**, 67, 69-75, from the appropriate amino acid (Scheme 3). The reductive alkylation can be accomplished at pH 5-7 with a variety of reducing agents, such as sodium triacetoxyborohydride or sodium cyanoborohydride in a solvent such as dichloroethane, methanol or dimethylformamide. The product X can be deprotected to give the final compounds XI with trifluoroacetic acid in methylene chloride. The final product XI is isolated in the salt form, for example, as a trifluoroacetate, hydrochloride or acetate salt, among others. The product diamine XI can further be selectively protected to obtain XII, which can subsequently be reductively alkylated with a second aldehyde to obtain XIII. Removal of the protecting
- 30

group, and conversion to cyclized products such as the dihydroimidazole XV can be accomplished by literature procedures.

Alternatively, the protected piperazine intermediate VII can be reductively alkylated with other aldehydes such as 1-trityl-4-imidazolyl-carboxaldehyde or 1-trityl-4-imidazolylacetaldehyde, to give products such as XVI (Scheme 4). The trityl protecting group can be removed from XVI to give XVII, or alternatively, XVI can first be treated with an alkyl halide then subsequently deprotected to give the alkylated imidazole XVIII. Alternatively, the intermediate VIII can be acylated or sulfonylated by standard techniques. The imidazole acetic acid XIX can be converted to the acetate XXI by standard procedures, and XXI can be first reacted with an alkyl halide, then treated with refluxing methanol to provide the regiospecifically alkylated imidazole acetic acid ester XXII. Hydrolysis and reaction with piperazine VIII in the presence of condensing reagents such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) leads to acylated products such as XXIV.

If the piperazine VIII is reductively alkylated with an aldehyde which also has a protected hydroxyl group, such as XXV in Scheme 6, the protecting groups can be subsequently removed to unmask the hydroxyl group (Schemes 6, 7). The alcohol can be oxidized under standard conditions to *e.g.* an aldehyde, which can then be reacted with a variety of organometallic reagents such as Grignard reagents, to obtain secondary alcohols such as XXIX. In addition, the fully deprotected amino alcohol XXX can be reductively alkylated (under conditions described previously) with a variety of aldehydes to obtain secondary amines, such as XXXI (Scheme 7), or tertiary amines.

The Boc protected amino alcohol XXVII can also be utilized to synthesize 2-aziridinylmethylpiperazines such as XXXII (Scheme 8). Treating XXVII with 1,1'-sulfonyldiimidazole and sodium hydride in a solvent such as dimethylformamide led to the formation of aziridine XXXII. The aziridine reacted in the presence of a nucleophile, such as a thiol, in the presence of base to yield the ring-opened product XXXIII.

In addition, the piperazine VIII can be reacted with aldehydes derived from amino acids such as O-alkylated tyrosines, according to standard procedures, to obtain compounds such as XXXIX. When R' is an aryl group, XXXIX can first be hydrogenated to unmask the phenol, and the amine group deprotected with acid to produce XL. Alternatively, the amine protecting group in XXXIX can be removed, and O-alkylated phenolic amines such as XLI produced.

Depending on the identity of the amino acid I, various side chains can be incorporated into the piperazine. For example when I is the Boc-protected β -benzyl ester of aspartic acid, the intermediate diketopiperazine XLII where $n=1$ and $R=\text{benzyl}$ is obtained, as shown in Scheme 10. Subsequent lithium aluminum hydride reduction reduces the ester to the alcohol XLIII, which can then be reacted with a variety of alkylating agents such as an alkyl iodide, under basic conditions, for example, sodium hydride in dimethylformamide or tetrahydrofuran. The resulting ether XLIV can then be carried on to final products as described in Schemes 3-9.

N-Aryl piperazines can be prepared as described in Scheme 11. An aryl amine XLV is reacted with *bis*-chloroethyl amine hydrochloride (XLVI) in refluxing *n*-butanol to furnish compounds XLVII. The resulting piperazines XLVII can then be carried on to final products as described in Schemes 3-9.

Piperazin-5-ones can be prepared as shown in Scheme 12. Reductive amination of Boc-protected amino aldehydes XLIX (prepared from I as described previously) gives rise to compound L. This is then reacted with bromoacetyl bromide under Schotten-Baumann conditions; ring closure is effected with a base such as sodium hydride in a polar aprotic solvent such as dimethylformamide to give LI. The carbamate protecting group is removed under acidic conditions such as trifluoroacetic acid in methylene chloride, or hydrogen chloride gas in methanol or ethyl acetate, and the resulting piperazine can then be carried on to final products as described in Schemes 3-9.

The isomeric piperazin-3-ones can be prepared as described in Scheme 13. The imine formed from arylcarboxamides LII and 2-

- aminoglycinal diethyl acetal (LIII) can be reduced under a variety of conditions, including sodium triacetoxymethylborohydride in dichloroethane, to give the amine LIV. Amino acids I can be coupled to amines LIV under standard conditions, and the resulting amide LV when treated with aqueous acid in tetrahydrofuran can cyclize to the unsaturated LVI. Catalytic hydrogenation under standard conditions gives the requisite intermediate LVII, which is elaborated to final products as described in Schemes 3-9.

- Access to alternatively substituted piperazines is described in Scheme 14. Following deprotection with trifluoroacetic acid, the N-benzyl piperazine V can be acylated with an aryl carboxylic acid. The resulting N-benzyl aryl carboxamide LIX can be hydrogenated in the presence of a catalyst to give the piperazine carboxamide LX which can then be carried on to final products as described in Schemes 3-9.

- Reaction Scheme 15 provides an illustrative example the synthesis of compounds of the instant invention wherein the substituents R^2 and R^3 are combined to form $-(CH_2)_n-$. For example, 1-aminocyclohexane-1-carboxylic acid LXI can be converted to the spiropiperazine LXVI essentially according to the procedures outlined in Schemes 1 and 2. The piperazine intermediate LXIX can be deprotected as before, and carried on to final products as described in Schemes 3-9. It is understood that reagents utilized to provide the substituent Y which is 2-(naphthyl) and the imidazolylalkyl substituent may be readily replaced by other reagents well known in the art and readily available to provide other N-substituents on the piperazine.

- The aldehyde XLIX from Scheme 12 can also be reductively alkylated with an aniline as shown in Scheme 16. The product LXXI can be converted to a piperazinone by acylation with chloroacetyl chloride to give LXXII, followed by base-induced cyclization to LXXIII. Deprotection, followed by reductive alkylation with a protected imidazole carboxaldehyde leads to LXXV, which can be alkylation with an arylmethylhalide to give the imidazolium salt LXXVI. Final removal of protecting groups by either solvolysis with a lower alkyl alcohol, such as methanol, or treatment with triethylsilane in

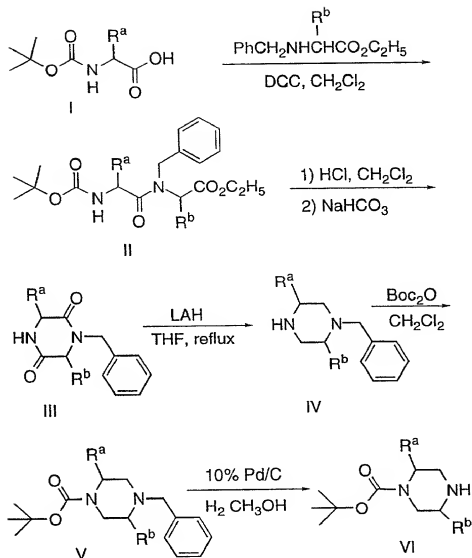
methylene chloride in the presence of trifluoroacetic acid gives the final product LXXXVII.

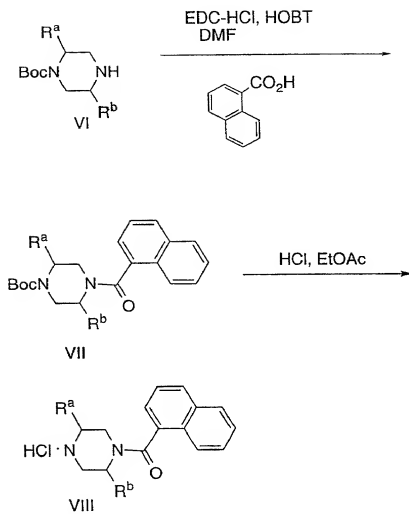
Scheme 17 illustrates the use of an optionally substituted homoserine lactone LXXIX to prepare a Boc-protected piperazinone LXXXII. Intermediate LXXXII may be deprotected and reductively alkylated or acylated as illustrated in the previous Schemes.

- Alternatively, the hydroxyl moiety of intermediate LXXXII may be mesylated and displaced by a suitable nucleophile, such as the sodium salt of ethane thiol, to provide an intermediate LXXXIII. Intermediate LXXXII may also be oxidized to provide the carboxylic acid on intermediate LXXXIV, which can be utilized form an ester or amide moiety.

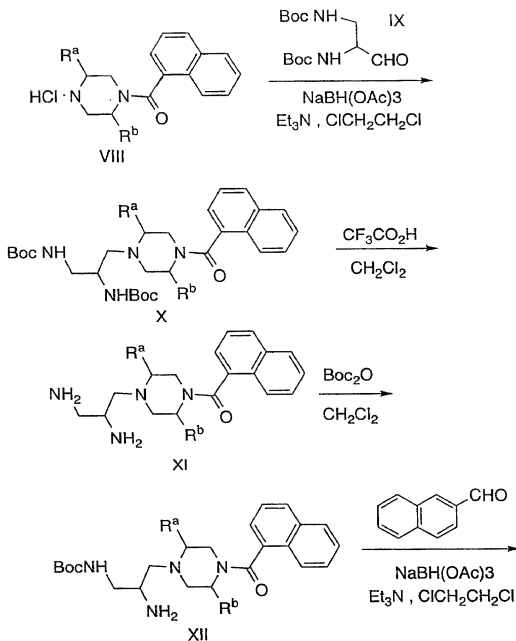
- Amino acids of the general formula LXXXVI which have a sidechain not found in natural amino acids may be prepared by the reactions illustrated in Scheme 18 starting with the readily prepared imine LXXXV.

- Schemes 19-22 illustrate syntheses of suitably substituted aldehydes useful in the syntheses of the instant compounds wherein the variable W is present as a pyridyl moiety. Similar synthetic strategies for preparing alkanols that incorporate other heterocyclic moieties for variable W are also well known in the art.

SCHEME 1

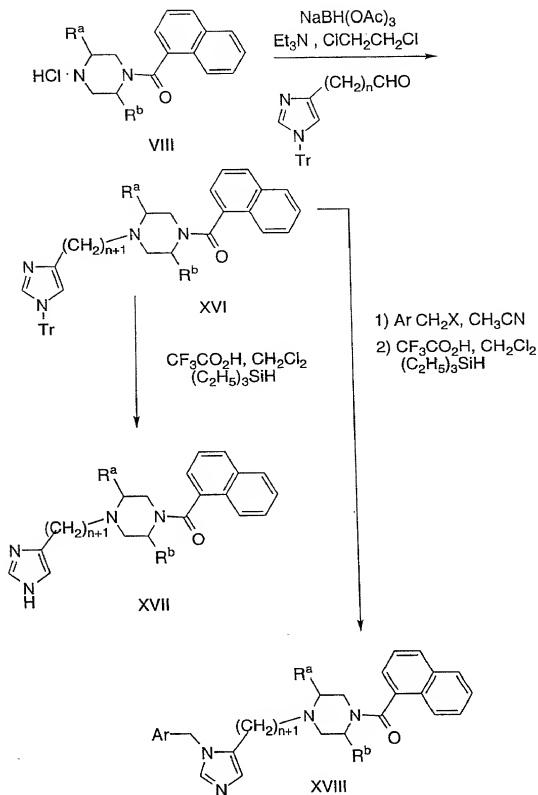
SCHEME 2

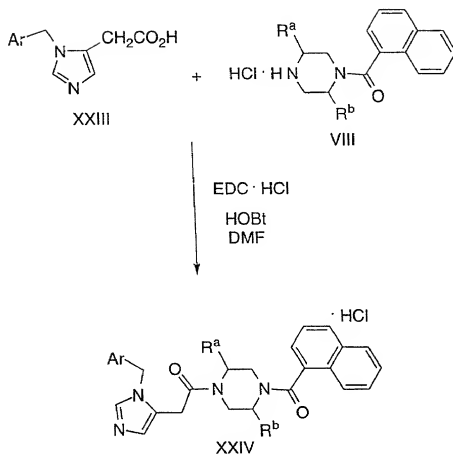
SCHEME 3



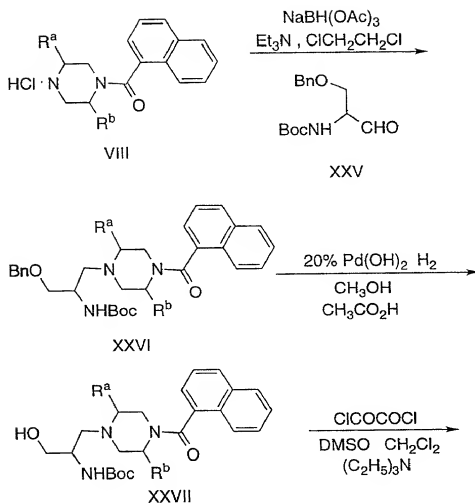


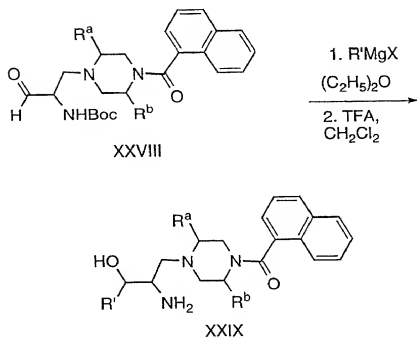
SCHEME 4

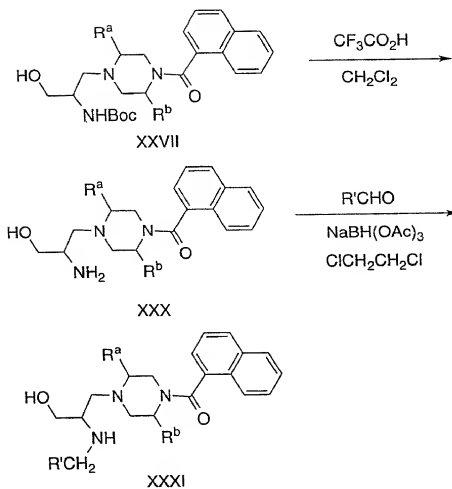


SCHEME 5 (continued)

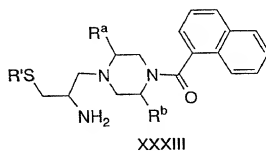
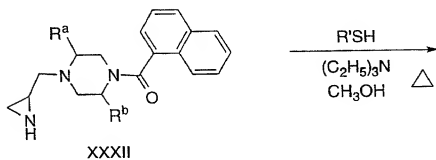
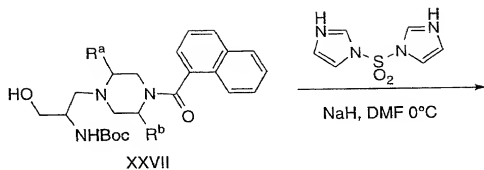
SCHEME 6



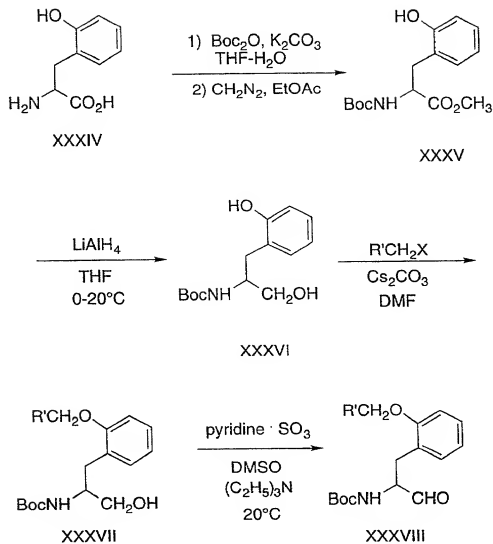
SCHEME 6 (CONTINUED)

SCHEME 7

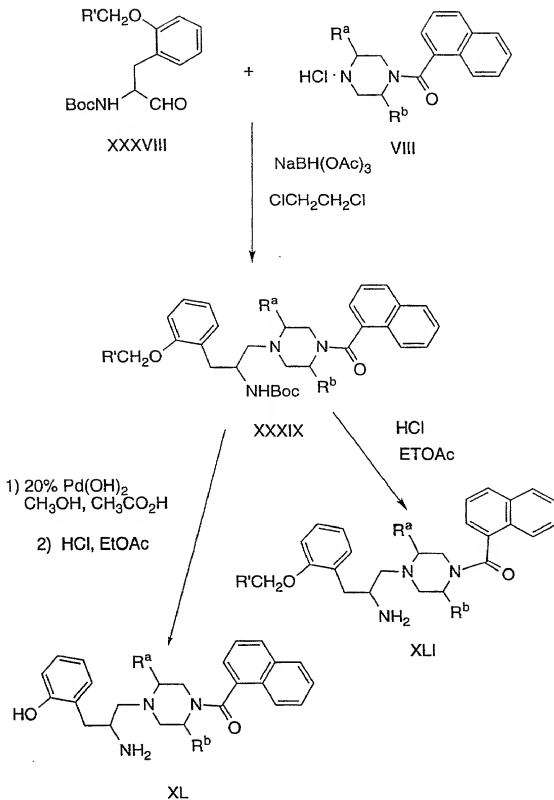
SCHEME 8

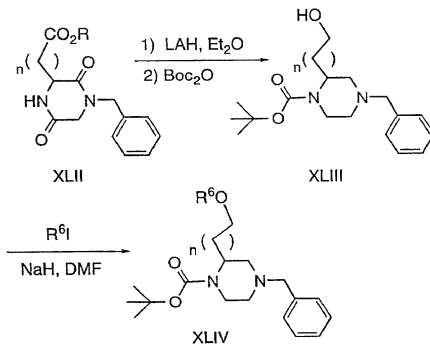


SCHEME 9

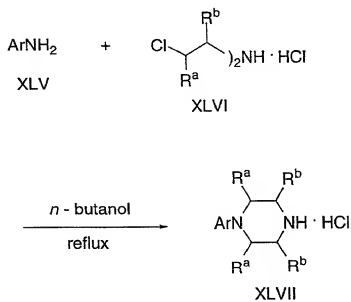


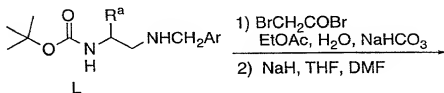
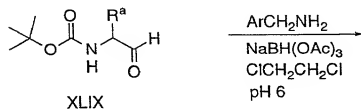
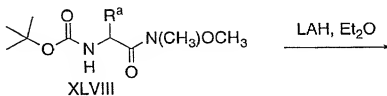
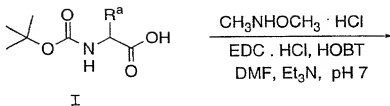
SCHEME 9 (continued)

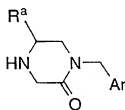
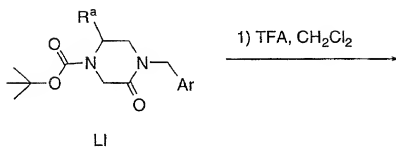


SCHEME 10

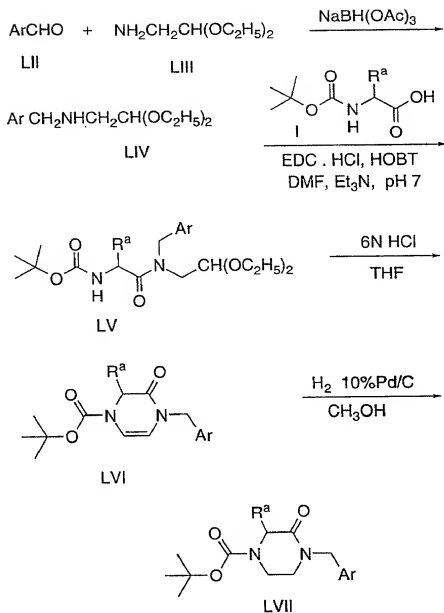
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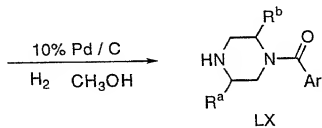
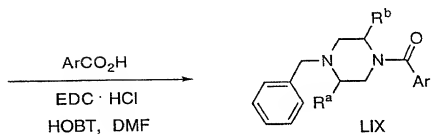
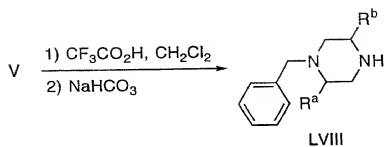
SCHEME 11

SCHEME 12

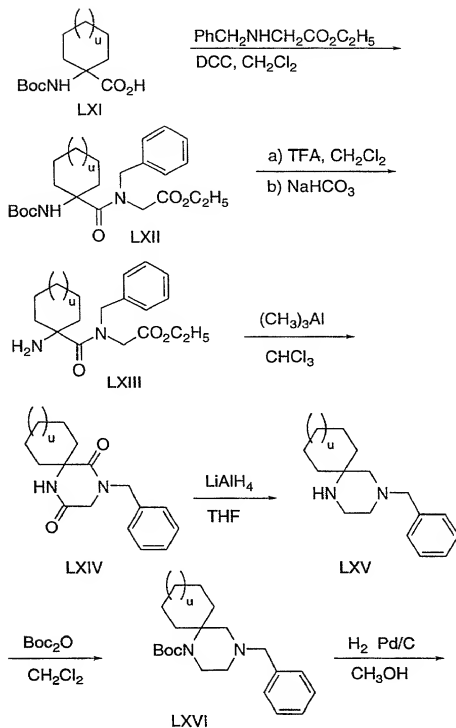
SCHEME 12 (CONT'D)

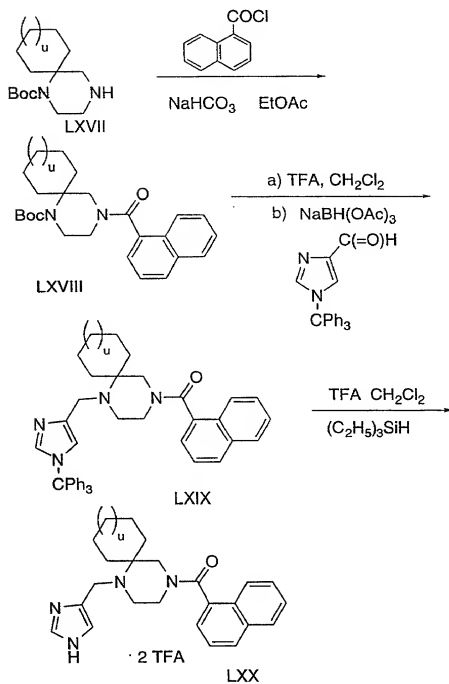
SCHEME 13

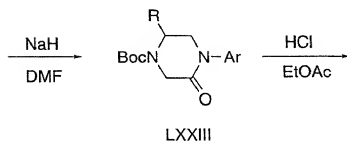
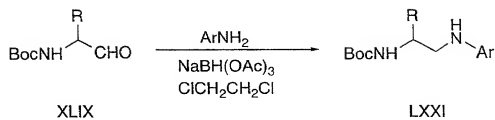


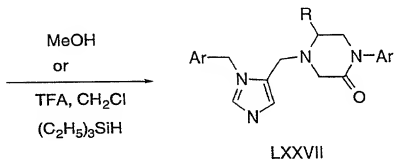
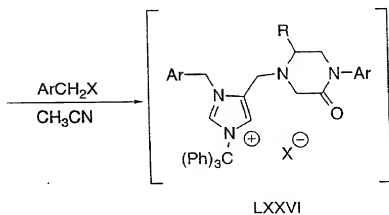
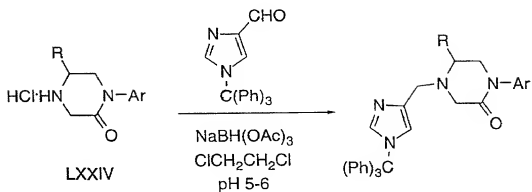
SCHEME 14

SCHEME 15

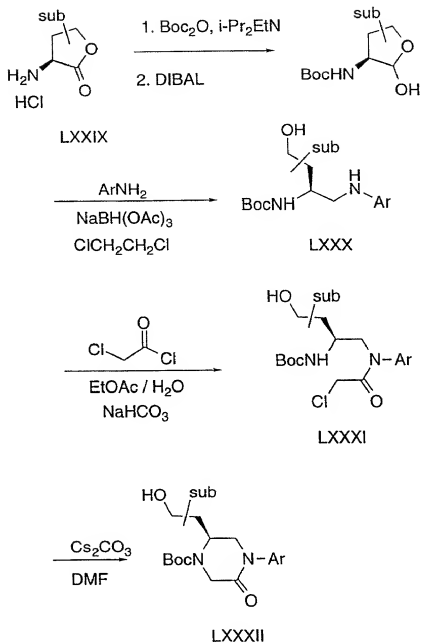


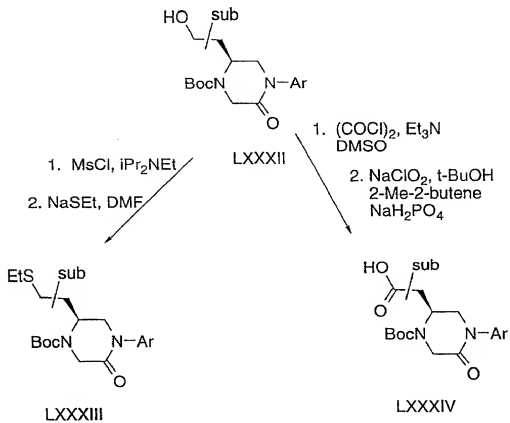
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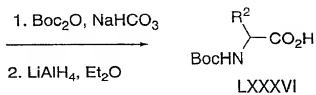
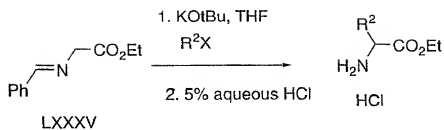
SCHEME 16

SCHEME 16 (continued)

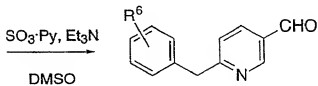
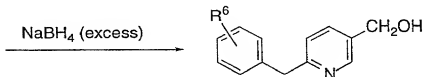
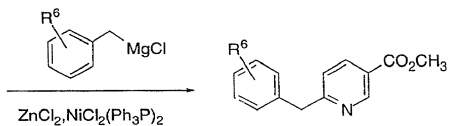
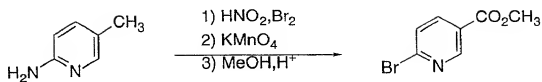
SCHEME 17



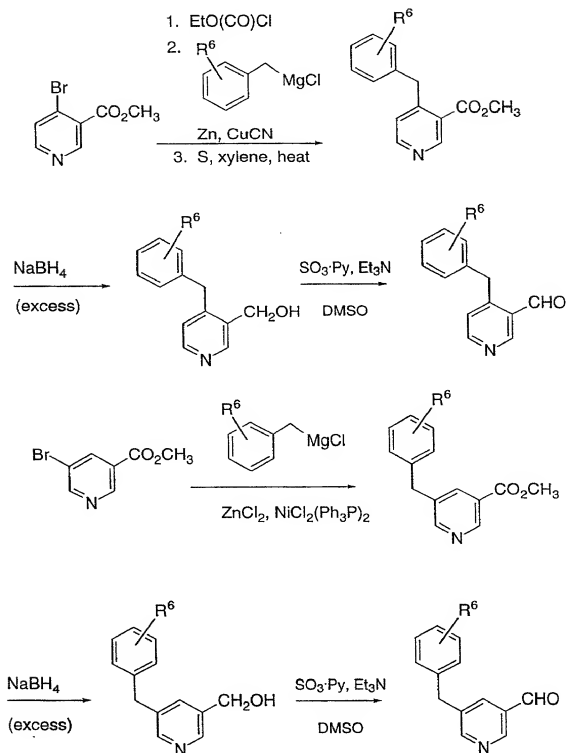
SCHEME 17 (continued)

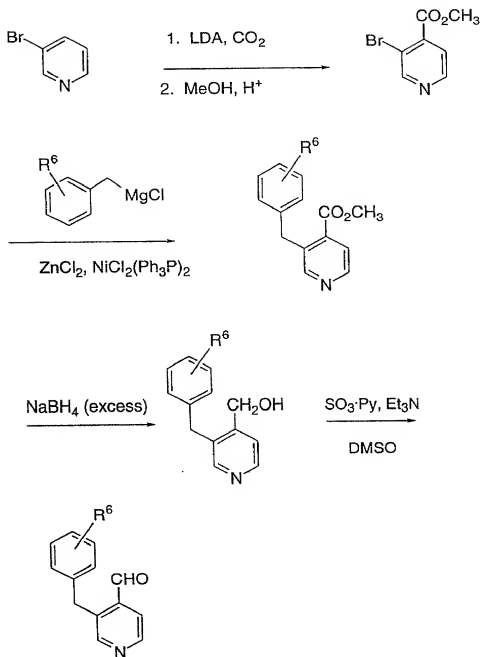
SCHEME 18

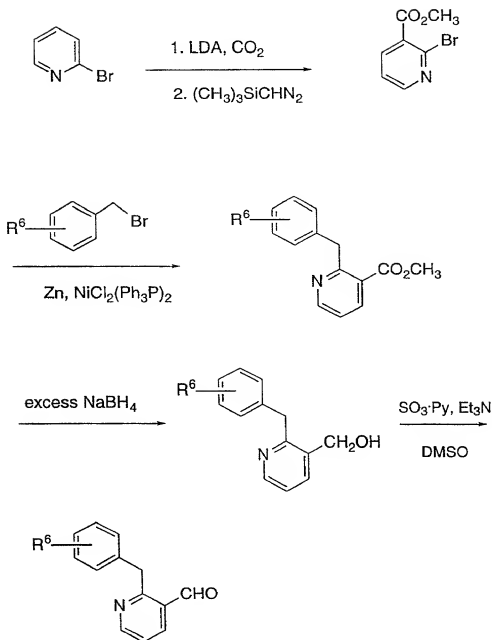
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REACTION SCHEME 19

REACTION SCHEME 20



REACTION SCHEME 21

REACTION SCHEME 22

5

The farnesyl transferase inhibitors of formula (II-d) can be synthesized in accordance with Schemes 23-36, in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the

experimental procedures. Substituents R², R⁶ and R⁸, as shown in the Schemes, represent the substituents R², R³, R⁴, R⁵, R^{6a}, R^{6b}, R^{6c}, R^{6d} and R⁸; although only one such R², R⁶ or R⁸ is present in the intermediates and products of the schemes, it is understood that the reactions shown are also applicable when such aryl or heteroaryl moieties contain multiple substituents. The compounds referred to in the Synopsis of Schemes 23-36 by Roman numerals are numbered starting sequentially with I and ending with XXV.

These reactions may be employed in a linear sequence to provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the alkylation reactions described in the Schemes. Aryl-aryl coupling is generally described in "Comprehensive Organic Functional Group Transformations," Katritsky et al. eds., pp 472-473, Pergamon Press (1995).

Synopsis of Schemes 23-36:

The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures, for the most part. Schemes 23-35 illustrate synthesis of the compounds of the formula II-d which incorporate a preferred benzylimidazolyl sidechain. In Scheme 23, for example, a biaryl intermediate that is not commercially available may be synthesized by methods known in the art. Thus, a suitably substituted phenyl boronic acid I may be reacted under Suzuki coupling conditions (*Pure Appl. Chem.*, 63:419 (1991)) with a suitably substituted halogenated benzoic acid, such as 4-bromobenzoic acid, to provide the biaryl carboxylic acid II. The acid may be reduced and the triflate of the intermediate alcohol III may be formed in situ and coupled to a suitably substituted benzylimidazolyl IV to provide, after deprotection, the instant compound V.

Schemes 24-27 illustrate other methods of synthesizing the key alcohol intermediates, which can then be processed as described in Scheme 23. Thus, Scheme 24 illustrates the analogous series of biaryl alcohol forming reactions starting with the halogenated biarylaldehyde.

Scheme 25 illustrates the reaction wherein the "terminal" phenyl moiety is employed in the Suzuki coupling as the halogenated reactant. Such a coupling reaction is also compatible when one of the reactants incorporates a suitably protected hydroxyl functionality as illustrated in Scheme 26.

Negishi chemistry (*Org. Synth.*, 66:67 (1988)) may also be employed to form the biaryl component of the instant compounds, as shown in Scheme 27. Thus, a suitably substituted zinc bromide adduct may be coupled to a suitably substituted aryl halide in the presence of nickel (II) to provide the biaryl VII. The aryl halide and the zinc bromide adduct may be selected based on the availability of the starting reagents.

Scheme 28 illustrates the preparation of a suitably substituted biphenylmethyl bromide which could also be utilized in the reaction with the protected imidazole as described in Scheme 1.

As illustrated in Scheme 29, the sequence of coupling reactions may be modified such that the biphenyl bond is formed last. Thus, a suitably substituted imidazole may first be alkylated with a suitably substituted benzyl halide to provide intermediate VIII. Intermediate VIII can then undergo Suzuki type coupling to a suitably substituted phenyl boronic acid.

Scheme 30 illustrates synthesis of an instant compound wherein a non-hydrogen R^{9b} is incorporated in the instant compound. Thus, a readily available 4-substituted imidazole IX may be selectively iodinated to provide the 5-iodoimidazole X. That imidazole may then be protected and coupled to a suitably substituted benzyl moiety to provide intermediate XI. Intermediate XI can then undergo the alkylation reactions that were described hereinabove.

Scheme 31 illustrates synthesis of instant compounds that incorporate a preferred imidazolyl moiety connected to the biaryl via an alkyl amino, sulfonamide or amide linker. Thus, the 4-aminoalkyl-imidazole XII, wherein the primary amine is protected as the phthalimide, is selectively alkylated then deprotected to provide the amine XIII. The amine XIII may then react under conditions well

known in the art with various activated biaryl moieties to provide the instant compounds shown.

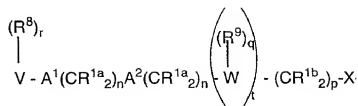
- Compounds of the instant invention wherein the $A^1(CR^{1a}_2)_nA^2(CR^{1a}_2)_n$ linker is oxygen may be synthesized by methods known in the art, for example as shown in Scheme 32. The suitably substituted phenol XIV may be reacted with methyl N-(cyano)methanimidate to provide the 4-phenoxyimidazole XV. After selective protection of one of the imidazolyl nitrogens, the intermediate XVI can undergo alkylation reactions as described for the benzylimidazoles hereinabove.

- Scheme 33 illustrates an analogous series of reactions wherein the $(CR^{1b}_2)_pX(CR^{1b}_2)_p$ linker of the instant compounds is oxygen. Thus, a suitably substituted haloaryl alcohol, such as, is reacted with methyl N-(cyano)methanimidate to provide intermediate XVI. Intermediate XVI is then protected and, if desired to form a compound of a preferred embodiment, alkylated with a suitably protected benzyl. The intermediate XVII can then be coupled to a second aryl moiety by Suzuki chemistry to provide the instant compound.

- Compounds of the instant invention wherein the $A^1(CR^{1a}_2)_nA^2(CR^{1a}_2)_n$ linker is a substituted methylene may be synthesized by the methods shown in Scheme 34. Thus, the N-protected imidazolyl iodide XVIII is reacted, under Grignard conditions with a suitably protected benzaldehyde to provide the alcohol XIX. Acylation, followed by the alkylation procedure illustrated in the Schemes above (in particular, Scheme 23) provides the instant compound XX. If other R^1 substituents are desired, the acetyl moiety can be manipulated as illustrated in the Scheme.

- Grignard chemistry may also be employed to form a substituted alkyl linker between the biaryl and the preferred W (imidazolyl) as shown in Scheme 35. Similar substituent manipulation as shown in Scheme 34 may be performed on the fully functionalized compound which incorporates an R^{1b} hydroxyl moiety.

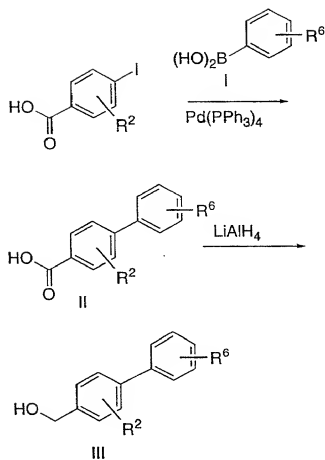
Scheme 36 illustrates reactions wherein the moiety



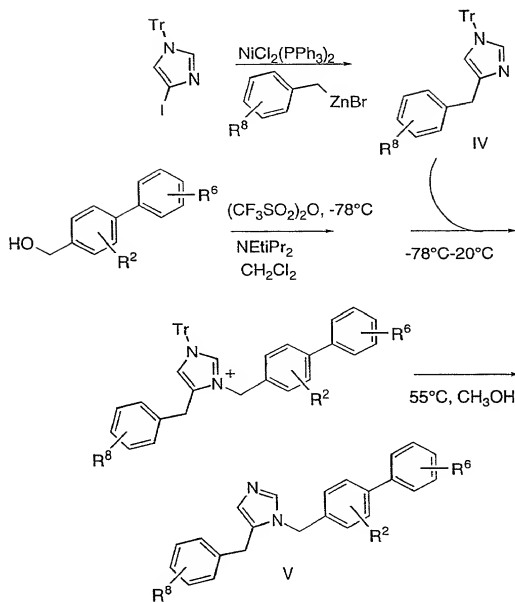
incorporated in the compounds of the instant invention is represented by other than a substituted imidazole-containing group.

- Thus, the intermediates whose synthesis are illustrated in Schemes hereinabove and other biheteroaryl intermediates obtained commercially or readily synthesized, can be coupled with a variety of aldehydes. The aldehydes can be prepared by standard procedures, such as that described by O. P. Goel, U. Krolls, M. Stier and S. Kesten in Organic Syntheses, **1988**, 67, 69-75, from the appropriate amino acid (Scheme 14). Grignard chemistry may be utilized, as shown in Scheme 36, to incorporate the biaryl moiety. Thus, a suitably substituted biaryl Grignard reagent is reacted with an aldehyde to provide the C-alkylated instant compound **XXI**. Compound **XXI** can be deoxygenated by methods known in the art, such as a catalytic hydrogenation, then deprotected with trifluoroacetic acid in methylene chloride to give the final compound **XXII**. The final product **XXII** may be isolated in the salt form, for example, as a trifluoroacetate, hydrochloride or acetate salt, among others. The product diamine **XXII** can further be selectively protected to obtain **XXIII**, which can subsequently be reductively alkylated with a second aldehyde to obtain **XXIV**. Removal of the protecting group, and conversion to cyclized products such as the dihydroimidazole **XXV** can be accomplished by literature procedures.

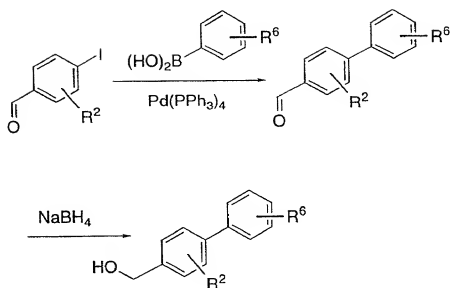
- Incorporation of other moieties via the appropriate aldehyde starting material may be performed as illustrated in Scheme 36 and the intermediates manipulated as illustrated above in Schemes 4-9.

SCHEME 23

SCHEME 23 (continued)

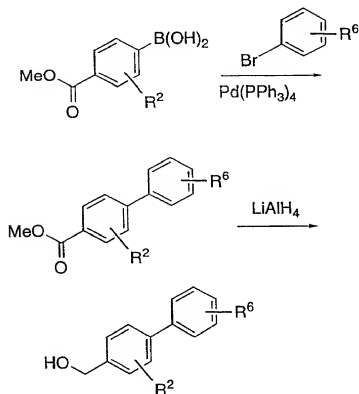


SCHEME 24

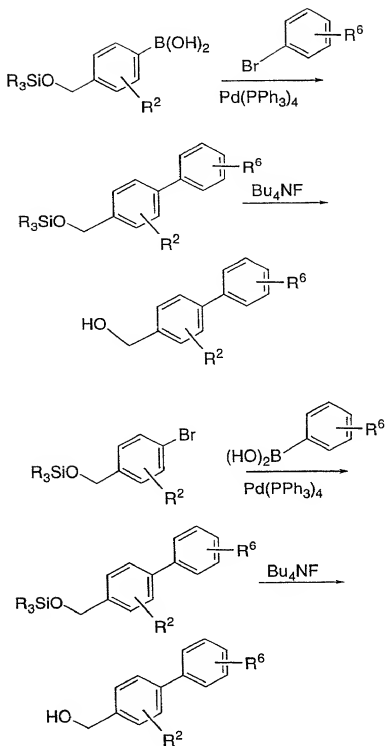


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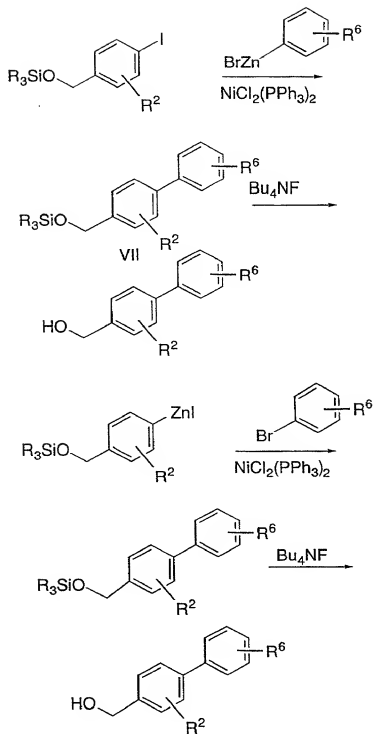
SCHEME 25

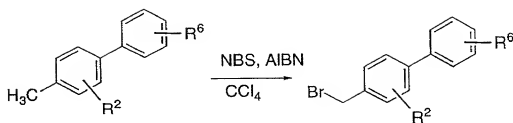


SCHEME 26

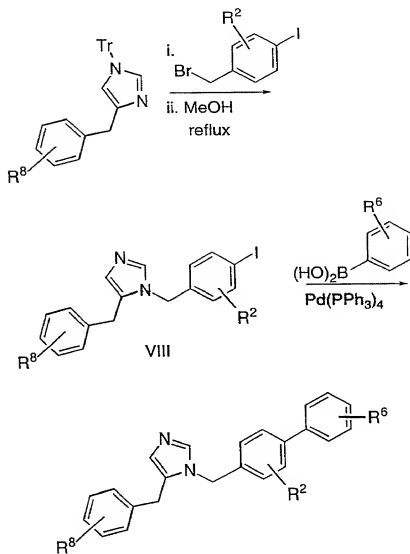


SCHEME 27

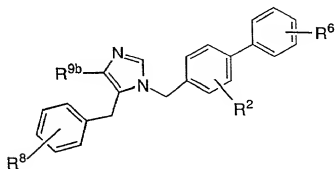
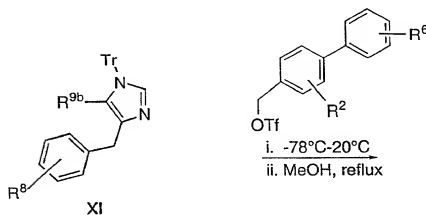
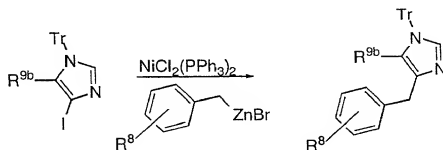
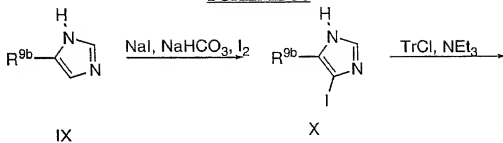


SCHEME 28

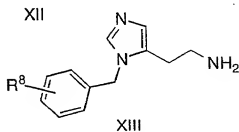
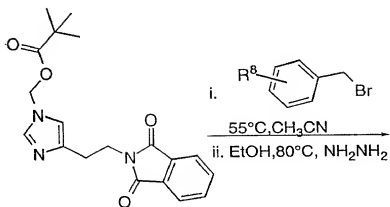
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SCHEME 29

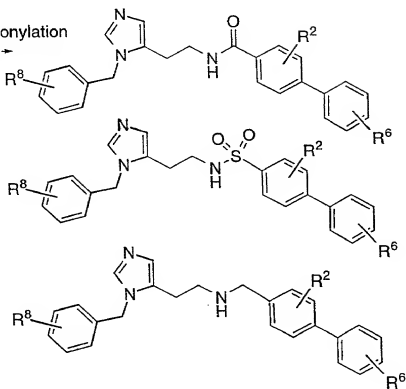
SCHEME 30

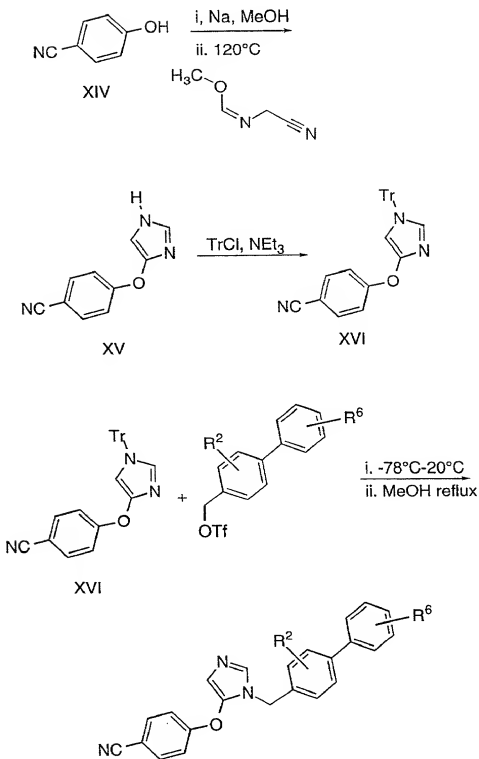


SCHEME 31

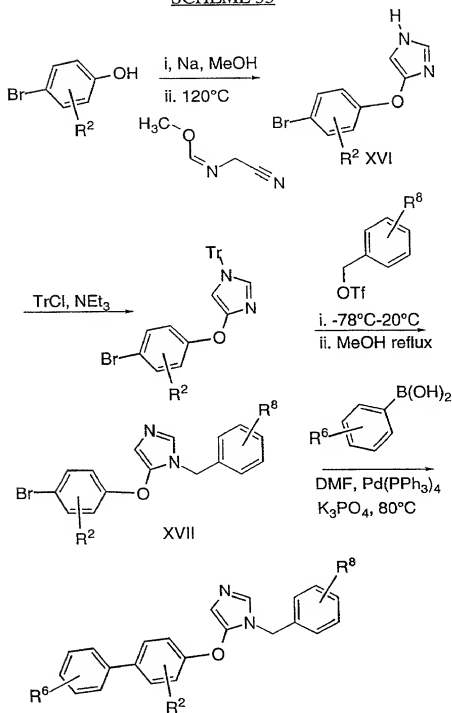


acylation, sulfonylation
or alkylation

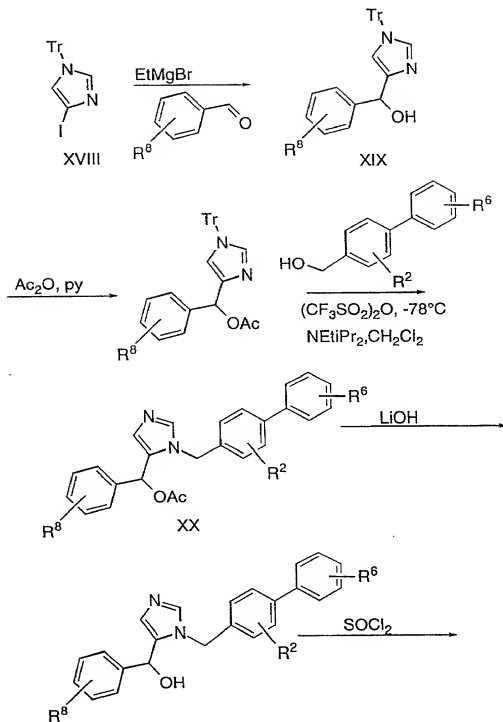


SCHEME 32

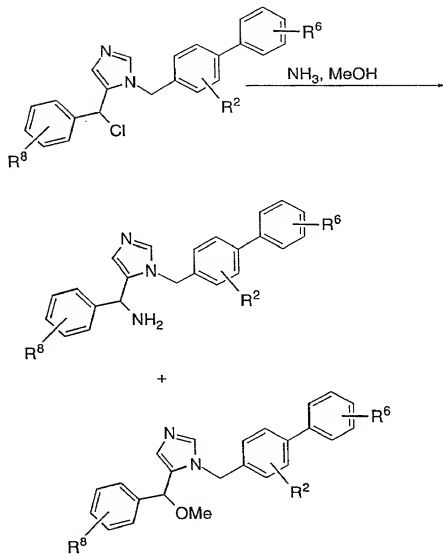
SCHEME 33



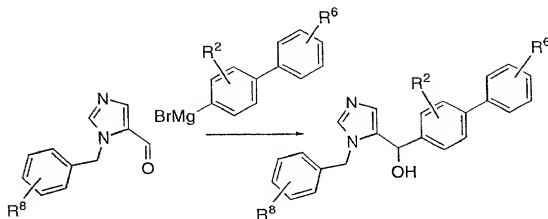
SCHEME 34



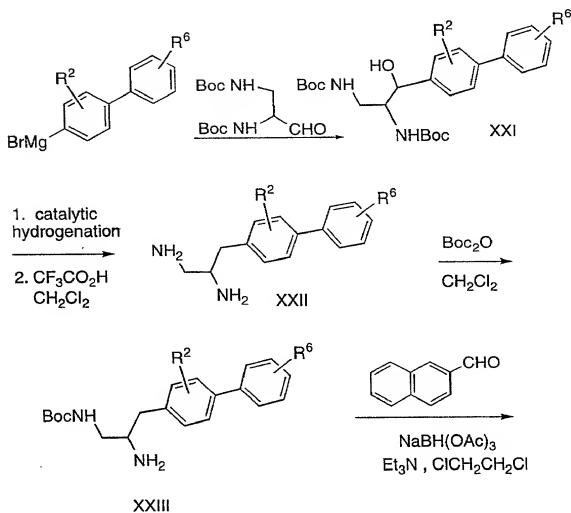
SCHEME 34 (continued)

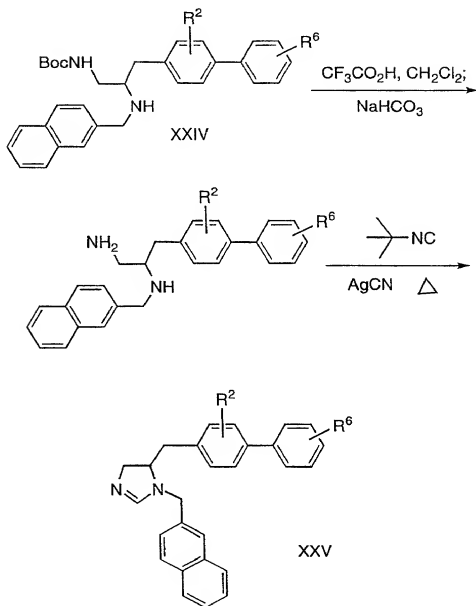


SCHEME 35



SCHEME 36



SCHEME 36 (continued)

The farnesyl transferase inhibitors of formula (II-e) can be synthesized in accordance with Schemes 37-52,

in addition to other standard manipulations such as ester hydrolysis,

- 5 cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures. Substituents R², R⁶ and R⁸, as shown in the Schemes, represent the substituents R², R³, R⁴, R⁵, R⁶ and R⁸; although only one such R², R⁶ or R⁸ is present in the intermediates and products of the schemes, it is understood that the
- 10 reactions shown are also applicable when such aryl or heteroaryl moieties contain multiple substituents. The compounds referred to in the Synopsis of Schemes 37-52 by Roman numerals are numbered starting sequentially with I and ending with XXV.

- These reactions may be employed in a linear sequence to
- 15 provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the alkylation reactions described in the Schemes. Other reactions useful in the preparation of heteroaryl moieties are described in "Comprehensive Organic Chemistry, Volume 4: Heterocyclic Compounds" ed. P.G. Sammes, Oxford (1979) and references therein. Aryl-aryl coupling is
- 20 generally described in "Comprehensive Organic Functional Group Transformations," Katritzky et al. eds., pp 472-473, Pergamon Press (1995).

25 Synopsis of Schemes 37-52:

- The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures, for the most part. Schemes 37-51 illustrate synthesis of the instant arylhetero-
- 30 aryl compound which incorporate a preferred benzylimidazolyl side-chain. Thus, in Scheme 37, for example, a arylheteroaryl intermediate that is not commercially available may be synthesized by methods known in the art. Thus, a suitably substituted pyridyl boronic acid I may be reacted under Suzuki coupling conditions (*Pure Appl. Chem.*, 63:419 (1991)) with a suitably substituted halogenated benzoic acid, such

as 4-bromobenzoic acid, to provide the arylheteroaryl carboxylic acid II. The acid may be reduced and the triflate of the intermediate alcohol III may be formed in situ and coupled to a suitably substituted benzyl-imidazolyl IV to provide, after deprotection, the instant compound V.

- 5 Schemes 38-41 illustrate other methods of synthesizing the key alcohol intermediates, which can then be processed as described in Scheme 1. Thus, Scheme 38 illustrates the analogous series of arylheteroaryl alcohol forming reactions starting with the halogenated arylaldehyde.

- 10 Scheme 39 illustrates the reaction wherein the "terminal" heteroaryl moiety is employed in the Suzuki coupling as the halogenated reactant. Such a coupling reaction is also compatible when one of the reactants incorporates a suitably protected hydroxyl functionality as illustrated in Scheme 40.

- 15 Negishi chemistry (*Org. Synth.*, 66:67 (1988)) may also be employed to form the arylheteroaryl component of the instant compounds, as shown in Scheme 41. Thus, a suitably substituted zinc bromide adduct may be coupled to a suitably substituted aryl halide in the presence of nickel (II) to provide the arylheteroaryl VII. The
20 heteroaryl halide and the zinc bromide adduct may be selected based on the availability of the starting reagents.

Scheme 42 illustrates the preparation of the suitably substituted arylheteroaryl methanol from the pyridyltoluene.

- 25 Scheme 43 illustrates the preparation of the suitably substituted pyrazinylaryl methanol starting with alanine.

As illustrated in Scheme 44, the sequence of coupling reactions may be modified such that the arylheteroaryl bond is formed last. Thus, a suitably substituted imidazole may first be alkylated with a suitably substituted benzyl halide to provide intermediate VIII.

- 30 Intermediate VIII can then undergo Suzuki type coupling to a suitably substituted heteroaryl boronic acid.

Scheme 45 illustrates synthesis of an instant compound wherein a non-hydrogen R^{9b} is incorporated in the instant compound. Thus, a readily available 4-substituted imidazole IX may be selectively

iodinated to provide the 5-iodoimidazole X. That imidazole may then be protected and coupled to a suitably substituted benzyl moiety to provide intermediate XI. Intermediate XI can then undergo the alkylation reactions that were described hereinabove.

5 Scheme 46 illustrates synthesis of instant compounds that incorporate a preferred imidazolyl moiety connected to the arylheteroaryl via an alkyl amino, sulfonamide or amide linker. Thus, the 4-aminoalkylimidazole XII, wherein the primary amine is protected as the phthalimide, is selectively alkylated then deprotected to provide
10 the amine XIII. The amine XIII may then react under conditions well known in the art with various activated arylheteroaryl moieties to provide the instant compounds shown.

 Compounds of the instant invention wherein the $A^1(CR^{1a}_2)_nA^2(CR^{1a}_2)_n$ linker is oxygen may be synthesized by
15 methods known in the art, for example as shown in Scheme 47. The suitably substituted phenol XIV may be reacted with methyl N-(cyano)methanimidate to provide the 4-phenoxyimidazole XV. After selective protection of one of the imidazolyl nitrogens, the intermediate XVI can undergo alkylation reactions as described
20 for the phenylmethylimidazoles hereinabove.

 Scheme 48 illustrates an analogous series of reactions wherein the $(CR^{1b}_2)_pX(CR^{1b}_2)_p$ linker of the instant compounds is oxygen. Thus, a suitably substituted haloaryl alcohol, such as 4-bromophenol, is reacted with methyl N-(cyano)methanimidate to
25 provide intermediate XVI. Intermediate XVI is then protected and, if desired to form a compound of a preferred embodiment, alkylated with a suitably protected benzyl. The intermediate XVII can then be coupled to a heteroaryl moiety by Suzuki chemistry to provide the instant compound.

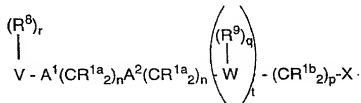
30 Compounds of the instant invention wherein the $A^1(CR^{1a}_2)_nA^2(CR^{1a}_2)_n$ linker is a substituted methylene may be synthesized by the methods shown in Scheme 49. Thus, the N-protected imidazolyl iodide XVIII is reacted, under Grignard conditions with a suitably protected benzaldehyde to provide the alcohol XIX. Acylation,

followed by the alkylation procedure illustrated in the Schemes above (in particular, Scheme 37) provides the instant compound XX. If other R^1 substituents are desired, the acetyl moiety can be manipulated as illustrated in the Scheme.

- 5 Addition of various nucleophiles to an imidazolyl aldehyde may also be employed to form a substituted alkyl linker between the arylheteroaryl and the preferred W (imidazolyl) as shown in Scheme 50. Thus a halogenated arylheteroaryl, such as 4-(3-pyridyl)bromobenzene, may undergo metal halogen exchange followed by reaction
10 with a suitably substituted imidazolyl aldehyde and acetylation to form the alcohol. Then, similar substituent manipulation as shown in Scheme 49 may be performed on a fully functionalized compound which incorporates an R^2 hydroxyl moiety.

- Scheme 51 illustrates the synthesis of a suitably substituted
15 pyrimidinebromobenzene, which may be employed in the reaction illustrated in Scheme 49. This reaction and other reactions useful in the preparation of heteroaryl moieties are described in "Comprehensive Organic Chemistry, Volume 4: Heterocyclic Compounds" ed. P.G. Sammes, Oxford (1979).

- 20 Schemes 52 illustrates reactions wherein the moiety

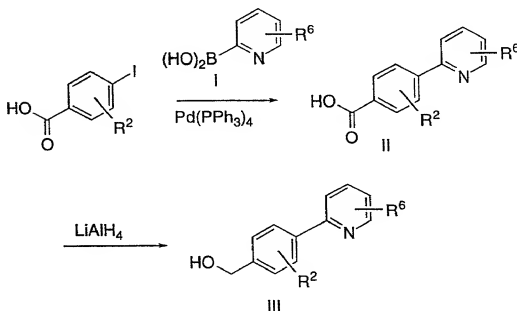


incorporated in the compounds of the instant invention is represented by other than a substituted imidazole-containing group.

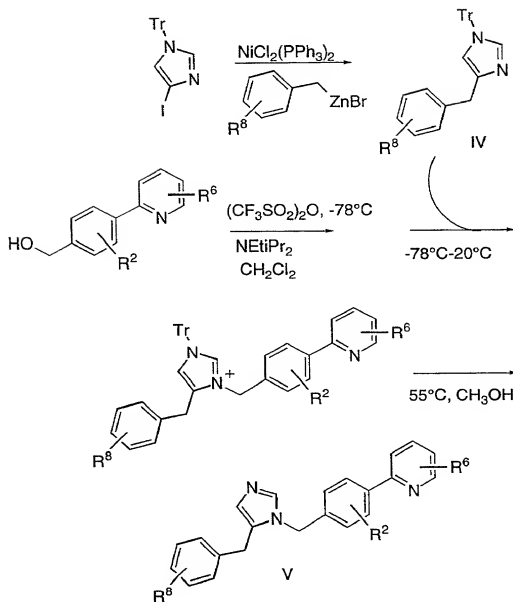
- Thus, the intermediates whose synthesis are illustrated in
25 Schemes hereinabove and other arylheteroaryl intermediates obtained commercially or readily synthesized, can be coupled with a variety of aldehydes. The aldehydes can be prepared by standard procedures, such as that described by O. P. Goel, U. Kroll, M. Stier and S. Kesten in Organic Syntheses, 1988, 67, 69-75, from the appropriate amino acid.
30 Metalation chemistry may be utilized, as shown in Scheme 52, to

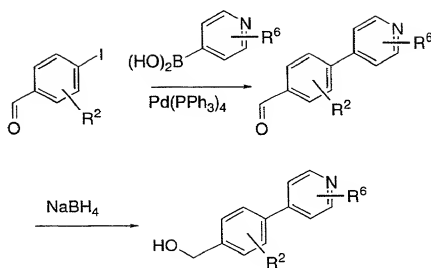
- incorporate the arylheteroaryl moiety. Thus, a suitably substituted arylheteroaryl lithium reagent, prepared in situ, is reacted with an aldehyde to provide the C-alkylated instant compound **XXI**. Compound **XXI** can be deoxygenated by methods known in the art, such as a catalytic hydrogenation, then deprotected with trifluoroacetic acid in methylene chloride to give the final compound **XXII**. The final product **XXII** may be isolated in the salt form, for example, as a trifluoroacetate, hydrochloride or acetate salt, among others. The product diamine **XXII** can further be selectively protected to obtain **XXIII**, which can subsequently be reductively alkylated with a second aldehyde to obtain **XXIV**. Removal of the protecting group, and conversion to cyclized products such as the dihydroimidazole **XXV** can be accomplished by literature procedures.
- Incorporation of other moieties via the appropriate aldehyde starting material may be performed as illustrated in Scheme 52 and the intermediates manipulated as illustrated above in Schemes 4-9.

SCHEME 37

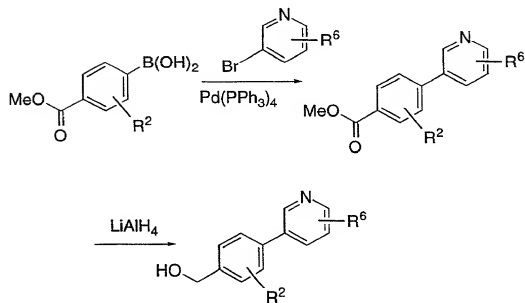


SCHEME 37 (continued)

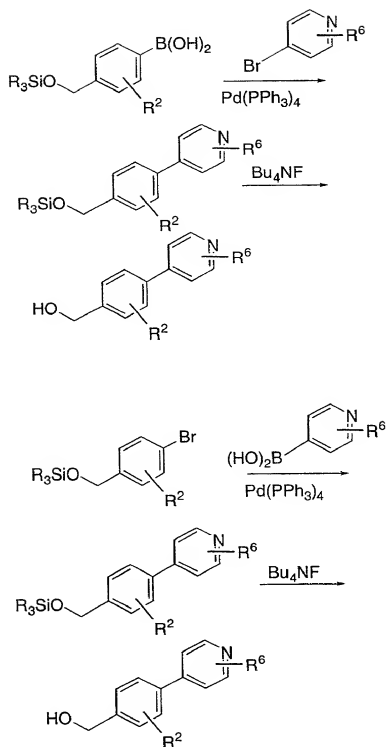


SCHEME 38

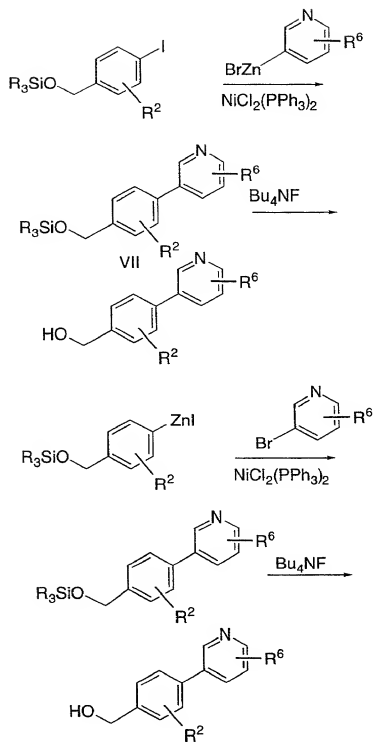
5

SCHEME 39

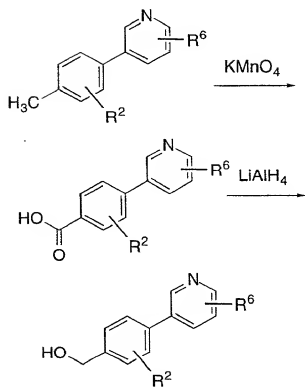
SCHEME 40



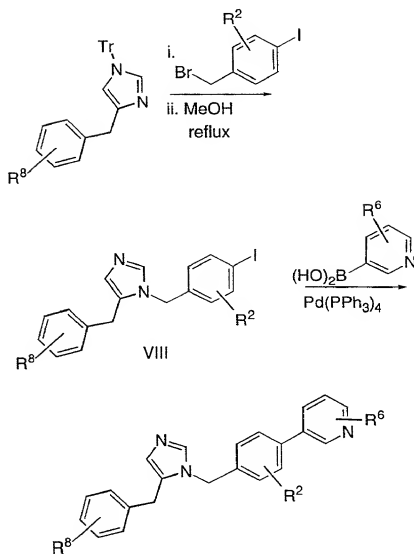
SCHEME 41



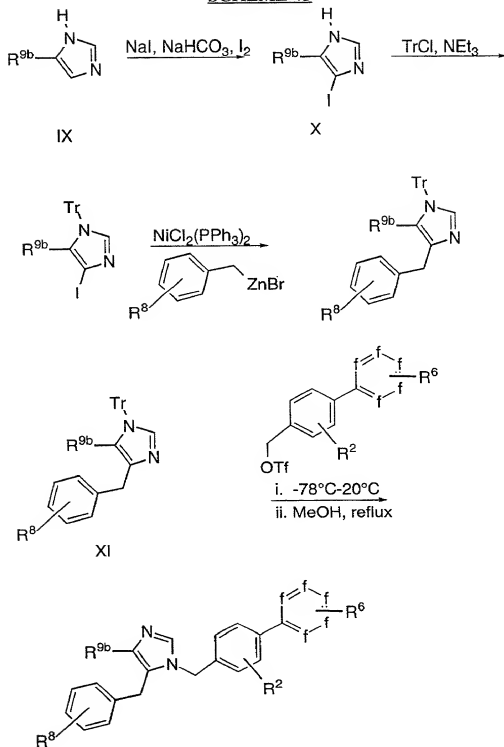
SCHEME 42



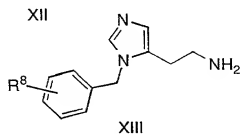
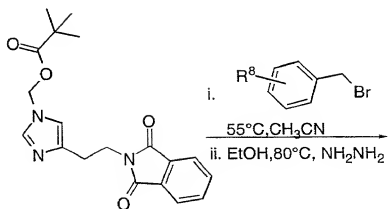
SCHEME 44



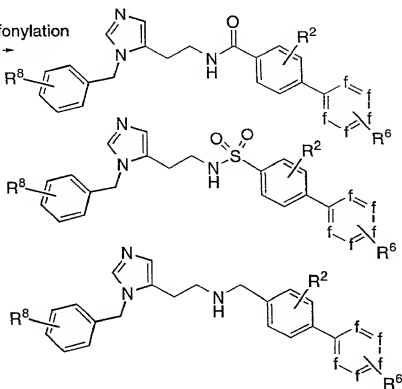
SCHEME 45

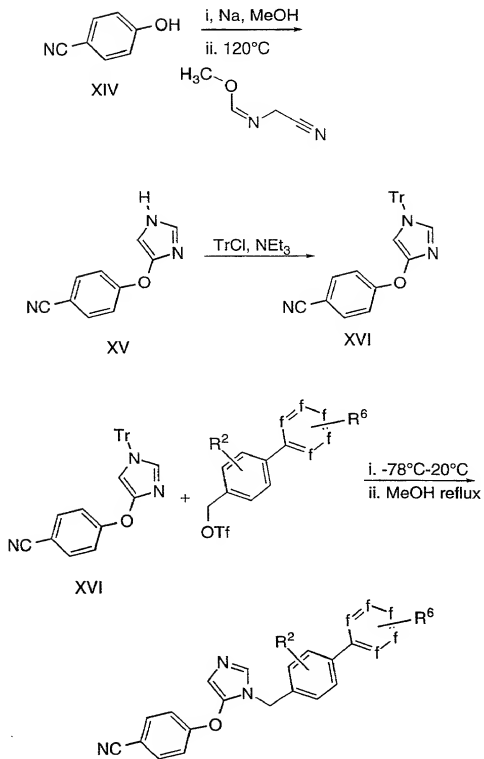


SCHEME 46

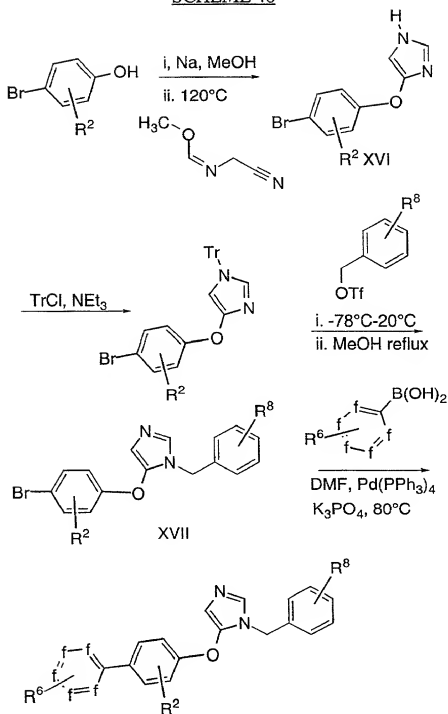


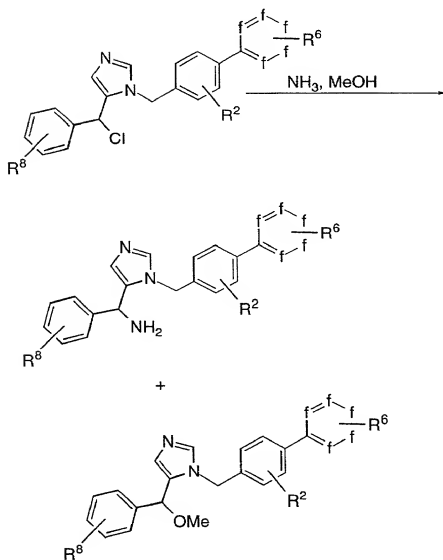
acylation, sulfonylation
or alkylation

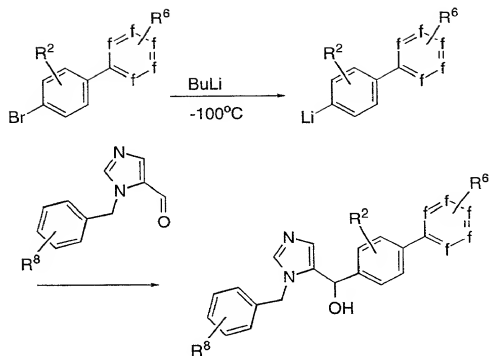
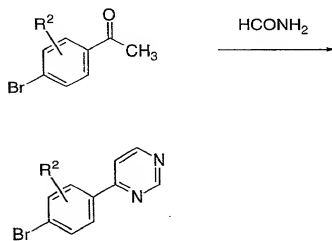


SCHEME 47

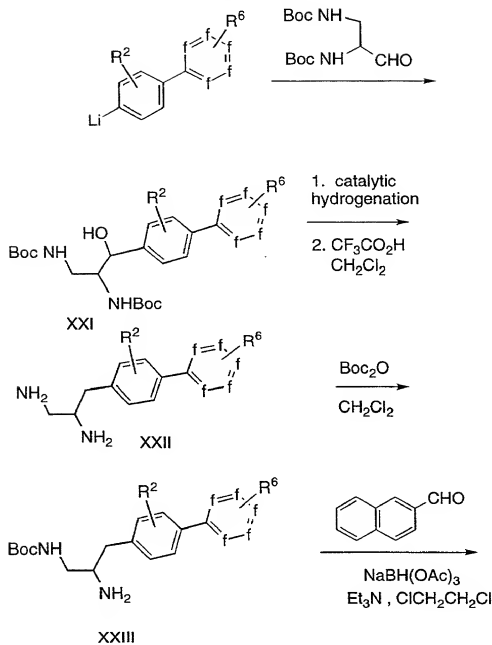
SCHEME 48



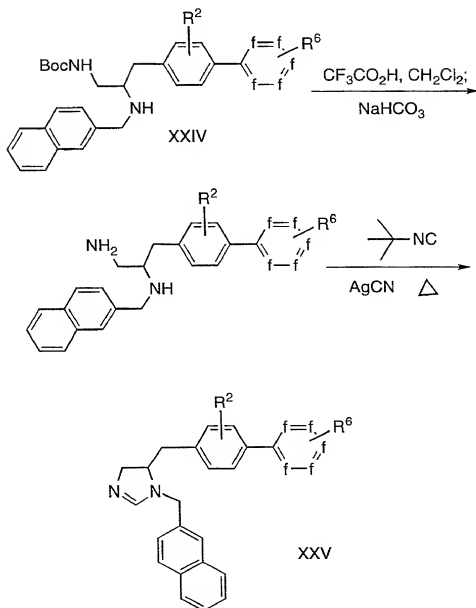
SCHEME 49 (continued)

SCHEME 50SCHEME 51

SCHEME 52



SCHEME 52 (continued)



- The farnesyl transferase inhibitors of formula (II-f) can be synthesized in accordance with Schemes 53-66, in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures. Substituents R³, R⁶ and R⁸, as shown in the Schemes, represent the substituents R³, R⁴, R⁵, R^{6a}, R^{6b}, R^{6c}, R^{6d}, R^{6e} and R⁸; although only one such R³, R⁶ or R⁸ is present in the intermediates and products of the schemes, it is understood that the reactions shown are also applicable when such aryl or heteroaryl moieties contain multiple substituents. The compounds referred to in the Synopsis of Schemes 53-66 by Roman numerals are numbered starting sequentially with I and ending with XXX.

- These reactions may be employed in a linear sequence to provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the alkylation reactions described in the Schemes. The reactions described in the Schemes are illustrative only and are not meant to be limiting. Other reactions useful in the preparation of heteroaryl moieties are described in "Comprehensive Organic Chemistry, Volume 4: Heterocyclic Compounds" ed. P.G. Sammes, Oxford (1979) and references therein. Aryl-aryl coupling is generally described in "Comprehensive Organic Functional Group Transformations," Katritzky et al. eds., pp 472-473, Pergamon Press (1995).

25 Synopsis of Schemes 53-66:

- The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures, for the most part. Schemes 53-64 illustrate synthesis of the instant aryl-heteroaryl compound which incorporate a preferred benzylimidazolyl sidechain. Thus, in Scheme 53, for example, a arylheteroaryl intermediate that is not commercially available may be synthesized by methods known in the art. Thus, a suitably substituted phenyl boronic acid I may be reacted under Suzuki coupling conditions (*Pure Appl. Chem.*, 63:419 (1991)) with a suitably substituted halogenated nicotinic

acid, such as 4-bromonicotinic acid, to provide the arylheteroaryl carboxylic acid II. The acid may be reduced and the triflate of the intermediate alcohol III may be formed in situ and coupled to a suitably substituted benzylimidazolyl IV to provide, after deprotection, the instant compound V.

Schemes 54-55 illustrate other methods of synthesizing the key alcohol intermediates, which can then be processed as described in Scheme 53. Thus, Scheme 54 illustrates the analogous series of arylheteroaryl alcohol forming reactions starting with the methyl nicotinate boronic acid and the "terminal" phenyl moiety employed in the Suzuki coupling as the halogenated reactant. Such a coupling reaction is also compatible when one of the reactants incorporates a suitably protected hydroxyl functionality as illustrated in Scheme 55.

Negishi chemistry (*Org. Synth.*, 66:67 (1988)) may also be employed to form the arylheteroaryl component of the instant compounds, as shown in Scheme 56. Thus, a suitably substituted zinc bromide adduct may be coupled to a suitably substituted heteroaryl halide in the presence of nickel (II) to provide the arylheteroaryl VII. The heteroaryl halide and the zinc bromide adduct may be selected based on the availability of the starting reagents.

Scheme 57 illustrates the preparation of a suitably substituted 3-hydroxymethyl-5-phenyl pyridine which could also be utilized in the reaction with the protected imidazole as described in Scheme 53. An Alternative preparation of a suitably substituted 5-hydroxymethyl-2-phenyl pyridine is also illustrated.

As illustrated in Scheme 58, the sequence of coupling reactions may be modified such that the aryl-heteroaryl bond is formed last. Thus, a suitably substituted imidazole may first be alkylated with a suitably substituted benzyl halide to provide intermediate VIII.

Intermediate VIII can then undergo Suzuki type coupling to a suitably substituted phenyl boronic acid.

Scheme 59 illustrates synthesis of an instant compound wherein a non-hydrogen R^{9b} is incorporated in the instant compound. Thus, a readily available 4-substituted imidazole IX may be selectively

iodinated to provide the 5-iodoimidazole X. That imidazole may then be protected and coupled to a suitably substituted benzyl moiety to provide intermediate XI. Intermediate XI can then undergo the alkylation reactions that were described hereinabove.

- 5 Scheme 60 illustrates synthesis of instant compounds that incorporate a preferred imidazolyl moiety connected to the biaryl via an alkyl amino, sulfonamide or amide linker. Thus, the 4-aminoalkyl-imidazole XII, wherein the primary amine is protected as the phthalimide, is selectively alkylated then deprotected to provide the
10 amine XIII. The amine XIII may then react under conditions well known in the art with various activated arylheteroaryl moieties to provide the instant compounds shown.

- Compounds of the instant invention wherein the $A^1(CR^1_2)_nA^2(CR^1_2)_n$ linker is oxygen may be synthesized by
15 methods known in the art, for example as shown in Scheme 61. The suitably substituted phenol XIV may be reacted with methyl N-(cyano)methanimidate to provide the 4-phenoxyimidazole XV. After selective protection of one of the imidazolyl nitrogens, the intermediate XVI can undergo alkylation reactions as described
20 for the benzylimidazoles hereinabove.

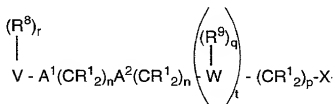
- Scheme 62 illustrates an analogous series of reactions wherein the $(CR^2_2)_pX(CR^2_2)_p$ linker of the instant compounds is oxygen. Thus, a suitably substituted halopyridinol, such as 3-chloro-
25 2-pyridinol, is reacted with methyl N-(cyano)methanimidate to provide intermediate XVI. Intermediate XVI is then protected and, if desired to form a compound of a preferred embodiment, alkylated with a suitably protected benzyl. The intermediate XVII can then be coupled to a aryl moiety by Suzuki chemistry to provide the instant compound.

- Compounds of the instant invention wherein the $A^1(CR^1_2)_nA^2(CR^1_2)_n$ linker is a substituted methylene may be
30 synthesized by the methods shown in Scheme 63. Thus, the N-protected imidazolyl iodide XVIII is reacted, under Grignard conditions with a suitably protected benzaldehyde to provide the alcohol XIX. Acylation, followed by the alkylation procedure illustrated in the Schemes above

(in particular, Scheme 53) provides the instant compound XX. If other R¹ substituents are desired, the acetyl moiety can be manipulated as illustrated in the Scheme.

- 5 Addition of various nucleophiles to an imidazolyl aldehyde may also be employed to form a substituted alkyl linker between the biheteroaryl and the preferred W (imidazolyl) as shown in Scheme 64. Thus a suitably substituted phenyl lithium can be reacted with pyridine to form the 2-substituted N-lithio-1,2-dihydropyridine XXa. Intermediate XXa can then react with an aldehyde to provide a suitably substituted instant compound. Similar substituent manipulation as shown in Scheme 63 may be performed on the fully functionalized compound which incorporates an R² hydroxyl moiety.

Scheme 65 illustrate reactions wherein the moiety



- 15 incorporated in the compounds of the instant invention is represented by other than a substituted imidazole-containing group.

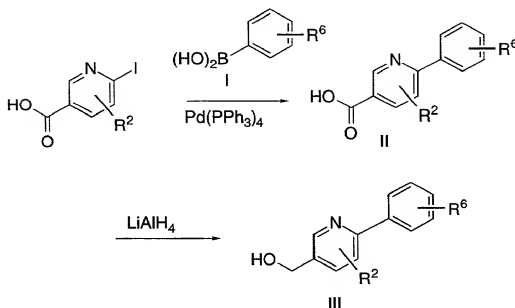
- Thus, the intermediates whose synthesis are illustrated in Schemes hereinabove and other arylheteroaryl intermediates obtained commercially or readily synthesized, can be coupled with a variety of aldehydes. The aldehydes can be prepared by standard procedures, such as that described by O. P. Goel, U. Krolls, M. Stier and S. Kesten in Organic Syntheses, **1988**, 67, 69-75, from the appropriate amino acid. Lithioheteroaryl chemistry may be utilized, as shown in Scheme 65, to incorporate the arylheteroaryl moiety. Thus, a suitably substituted arylheteroaryl N-lithio reagent is reacted with an aldehyde to provide the C-alkylated instant compound XXI. Compound XXI can be deoxygenated by methods known in the art, such as a catalytic hydrogenation, then deprotected with trifluoroacetic acid in methylene chloride to give the final compound XXII. The final product XXII may be isolated in the salt form, for example, as a trifluoroacetate,

- hydrochloride or acetate salt, among others. The product diamine **XXII** can further be selectively protected to obtain **XXIII**, which can subsequently be reductively alkylated with a second aldehyde to obtain **XXIV**. Removal of the protecting group, and conversion to cyclized products such as the dihydroimidazole **XXV** can be accomplished by literature procedures.

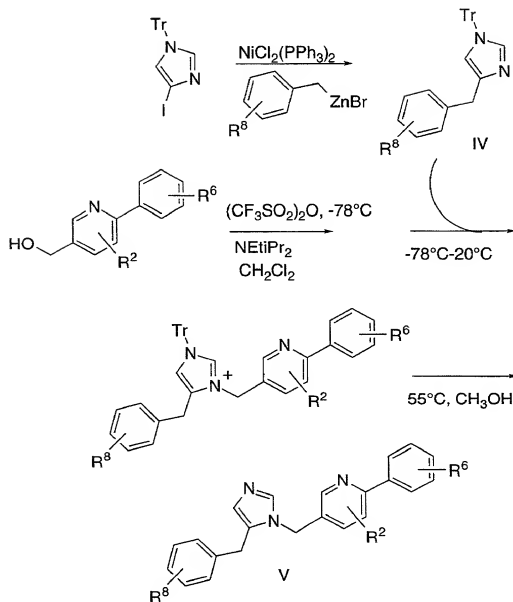
- If the arylheteroaryl subunit reagent is reacted with an aldehyde which also has a protected hydroxyl group, such as **XXVI** in Scheme 66, the protecting groups can be subsequently removed to unmask the hydroxyl group. The alcohol can be oxidized under standard conditions to *e.g.* an aldehyde, which can then be reacted with a variety of organometallic reagents such as alkyl lithium reagents, to obtain secondary alcohols such as **XXX**.

- Incorporation of other moieties via the appropriate aldehyde starting material may be performed as illustrated in Scheme 65-66 and the intermediates manipulated as illustrated above in Schemes 4-9.

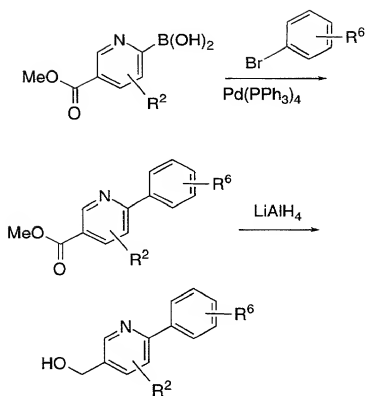
SCHEME 53



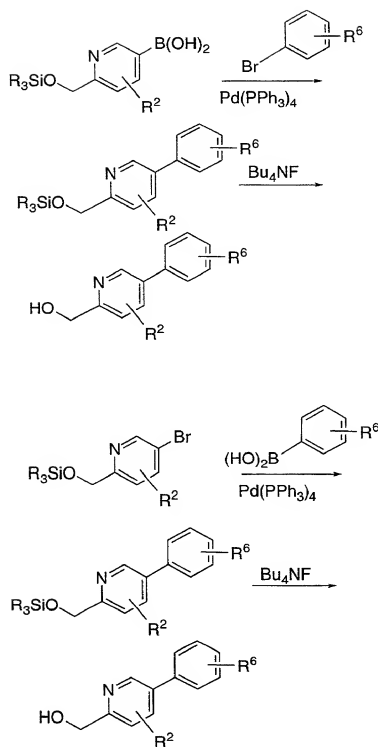
SCHEME 53 (continued)



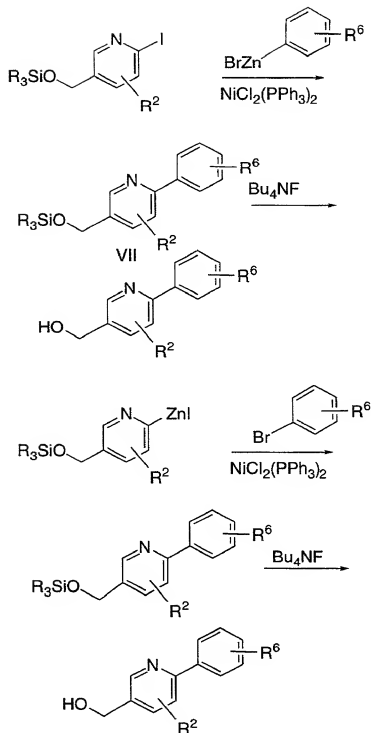
SCHEME 54



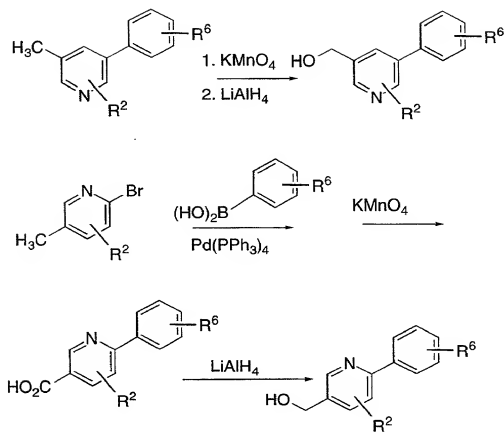
SCHEME 55



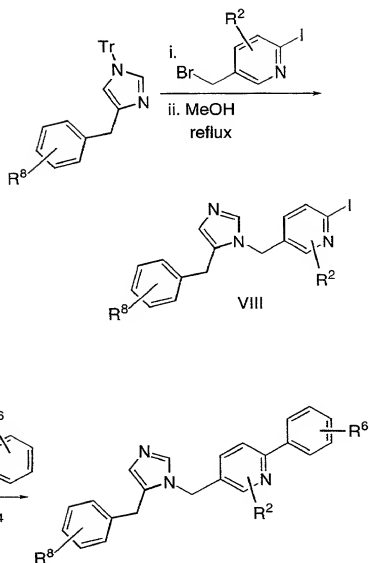
SCHEME 56



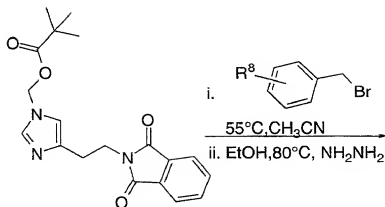
SCHEME 57



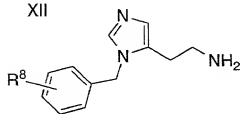
SCHEME 58



SCHEME 60

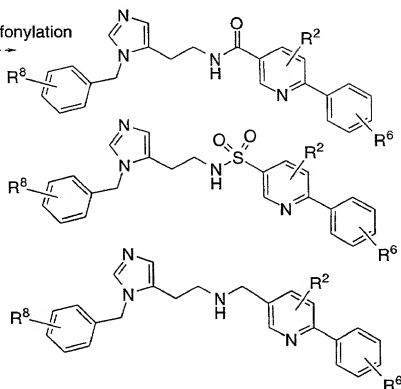


XII

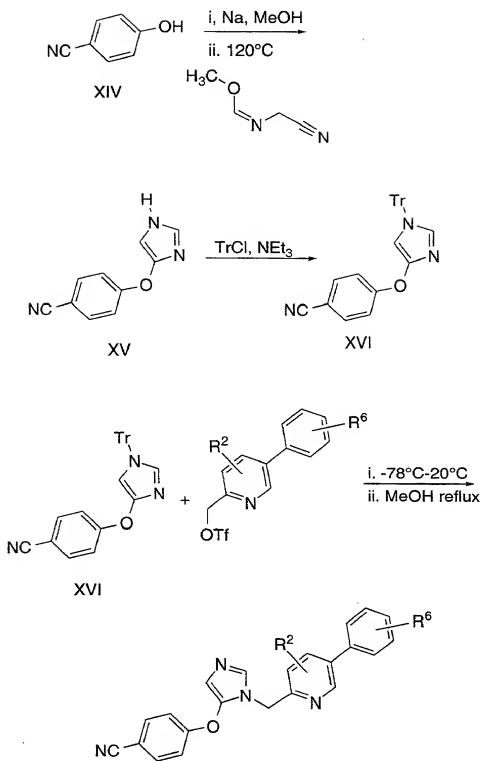


XIII

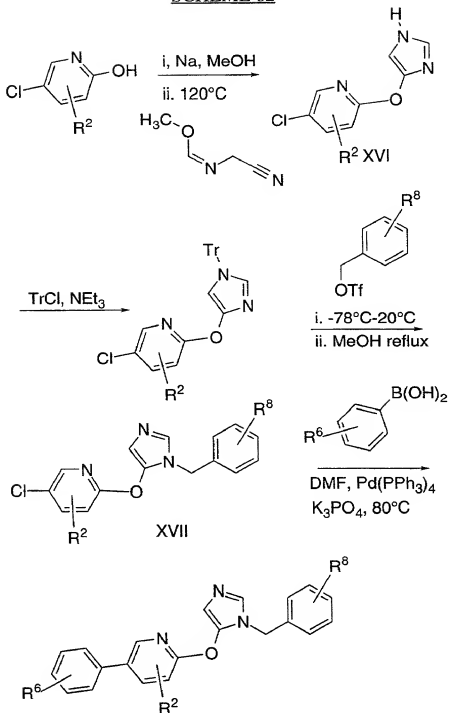
acylation, sulfonylation
or alkylation



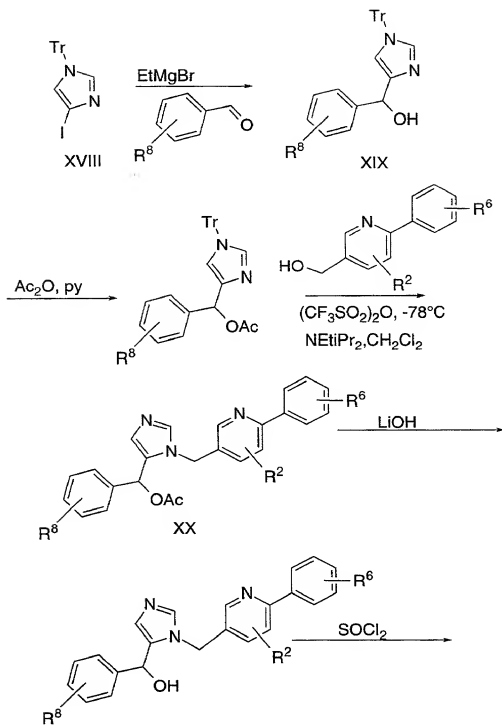
SCHEME 61

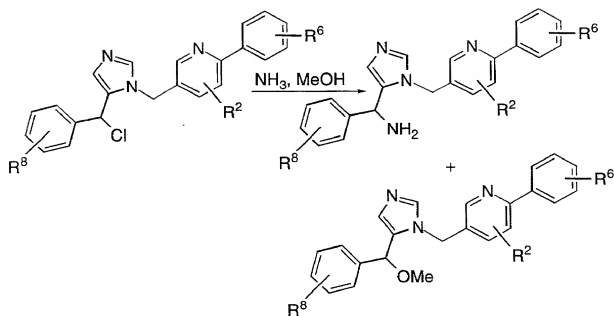
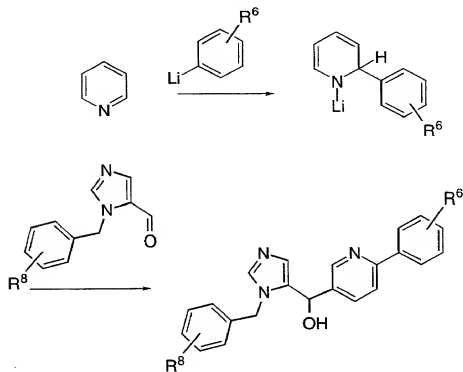


SCHEME 62

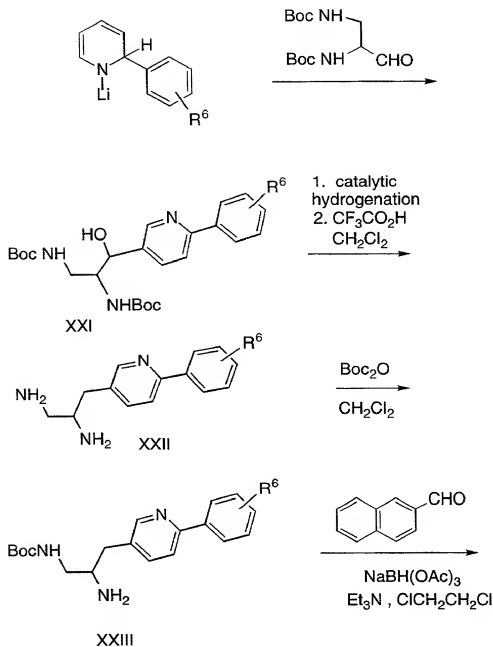


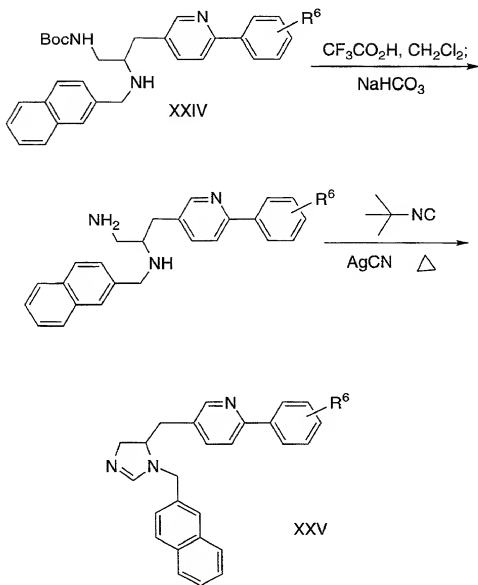
SCHEME 63



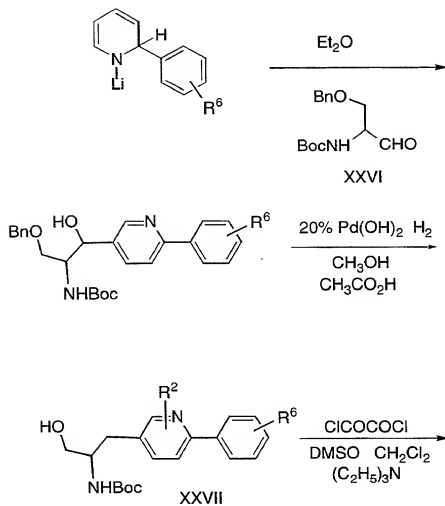
SCHEME 63 (continued)SCHEME 64

SCHEME 65

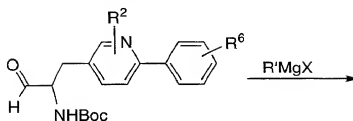


SCHEME 65 (continued)

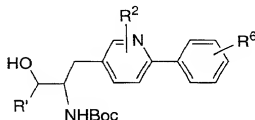
SCHEME 66



SCHEME 66 (continued)



XXIX



XXX

- The farnesyl transferase inhibitors of formula (II-g) can be synthesized in accordance with Schemes 67-78,
- 5 in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures. Substituents R³, R⁶ and R⁸, as shown in the Schemes, represent the substituents R³, R⁴, R⁵, R⁶ and R⁸; although only one such R³, R⁶ or R⁸ is present in the intermediates and products of the schemes, it is understood that the reactions shown are also applicable when such aryl or heteroaryl moieties contain multiple substituents. The compounds referred to in the Synopsis of Schemes 67-78 by Roman numerals are numbered
- 10 starting sequentially with I and ending with XX.
- 15

- These reactions may be employed in a linear sequence to provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the alkylation reactions described in the Schemes. The reactions described in the
- 20 Schemes are illustrative only and are not meant to be limiting. Other

reactions useful in the preparation of heteroaryl moieties are described in "Comprehensive Organic Chemistry, Volume 4: Heterocyclic Compounds" ed. P.G. Sammes, Oxford (1979) and references therein. Aryl-aryl coupling is generally described in "Comprehensive Organic Functional Group Transformations," Katritzky et al. eds., pp 472-473, Pergamon Press (1995).

Synopsis of Schemes 67-78:

The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures, for the most part. Schemes 67-78 illustrate synthesis of the instant biheteroaryl compound which incorporate a preferred benzylimidazolyl sidechain. Thus, in Scheme 67, for example, a biheteroaryl intermediate that is not commercially available may be synthesized by methods known in the art. Thus, a suitably substituted pyridyl boronic acid I may be reacted under Suzuki coupling conditions (*Pure Appl. Chem.*, 63:419 (1991)) with a suitably substituted halogenated nicotinic acid, such as 4-bromonicotinic acid, to provide the biheteroaryl carboxylic acid II. The acid may be reduced and the triflate of the intermediate alcohol III may be formed in situ and coupled to a suitably substituted benzylimidazolyl IV to provide, after deprotection, the instant compound V.

Schemes 68-71 illustrate other methods of synthesizing the key alcohol intermediates, which can then be processed as described in Scheme 67. Thus, Scheme 68 illustrates the analogous series of biheteroaryl alcohol forming reactions starting with the methyl nicotinate boronic acid and the "terminal" heteroaryl moiety employed in the Suzuki coupling as the halogenated reactant. Such a coupling reaction is also compatible when one of the reactants incorporates a suitably protected hydroxyl functionality as illustrated in Scheme 69.

Negishi chemistry (*Org. Synth.*, 66:67 (1988)) may also be employed to form the biheteroaryl component of the instant compounds, as shown in Scheme 70. Thus, a suitably substituted zinc bromide adduct may be coupled to a suitably substituted heteroaryl halide in the presence of nickel (II) to provide the biheteroaryl VII. The heteroaryl

halide and the zinc bromide adduct may be selected based on the availability of the starting reagents.

Scheme 71 illustrates the preparation of the pyridylmethanol intermediate starting with the 3-methyl pyridine.

- 5 As illustrated in Scheme 72, the sequence of coupling reactions may be modified such that the heteroaryl-heteroaryl bond is formed last. Thus, a suitably substituted imidazole may first be alkylated with a suitably substituted benzyl halide to provide intermediate VIII. Intermediate VIII can then undergo Suzuki type
10 coupling to a suitably substituted pyridyl boronic acid.

- Scheme 73 illustrates synthesis of an instant compound wherein a non-hydrogen R^{9b} is incorporated in the instant compound. Thus, a readily available 4-substituted imidazole IX may be selectively iodinated to provide the 5-iodoimidazole X. That imidazole may then
15 be protected and coupled to a suitably substituted benzyl moiety to provide intermediate XI. Intermediate XI can then undergo the alkylation reactions that were described hereinabove.

- Scheme 74 illustrates synthesis of instant compounds that incorporate a preferred imidazolyl moiety connected to the biaryl via an alkyl amino, sulfonamide or amide linker. Thus, the 4-aminoalkyl-
20 imidazole XII, wherein the primary amine is protected as the phthalimide, is selectively alkylated then deprotected to provide the amine XIII. The amine XIII may then react under conditions well known in the art with various activated biheteroaryl moieties to
25 provide the instant compounds shown.

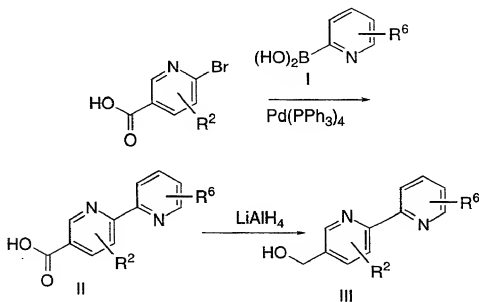
- Compounds of the instant invention wherein the $A^1(CR^1_2)_nA^2(CR^1_2)_n$ linker is oxygen may be synthesized by methods known in the art, for example as shown in Scheme 75. The suitably substituted phenol XIV may be reacted with methyl
30 N-(cyano)methanimidate to provide the 4-phenoxyimidazole XV. After selective protection of one of the imidazolyl nitrogens, the intermediate XVI can undergo alkylation reactions as described for the benzylimidazoles hereinabove.

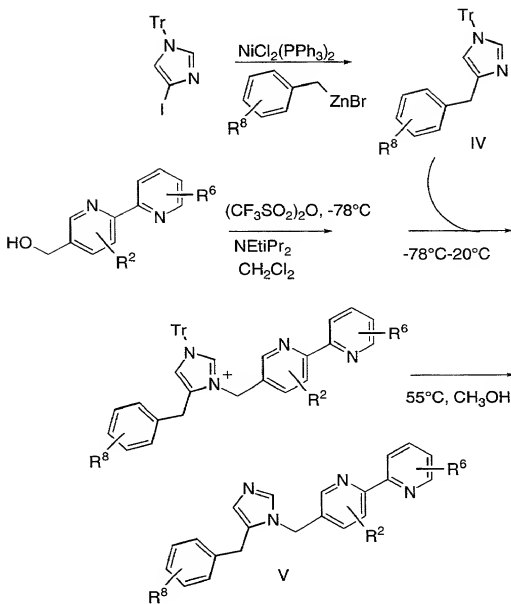
Scheme 76 illustrates an analogous series of reactions wherein the $(CR^2)_pX(CR^2)_p$ linker of the instant compounds is oxygen. Thus, a suitably substituted halopyridinol, such as 3-chloro-2-pyridinol, is reacted with methyl N-(cyano)methanimidate to provide intermediate XVI. Intermediate XVI is then protected and, if desired to form a compound of a preferred embodiment, alkylated with a suitably protected benzyl. The intermediate XVII can then be coupled to a heteroaryl moiety by Suzuki chemistry to provide the instant compound.

- Compounds of the instant invention wherein the $A^1(CR^1)_nA^2(CR^1)_n$ linker is a substituted methylene may be synthesized by the methods shown in Scheme 77. Thus, the N-protected imidazolyl iodide XVIII is reacted, under Grignard conditions with a suitably protected benzaldehyde to provide the alcohol XIX. Acylation, followed by the alkylation procedure illustrated in the Schemes above (in particular, Scheme 67) provides the instant compound XX. If other R^1 substituents are desired, the acetyl moiety can be manipulated as illustrated in the Scheme.

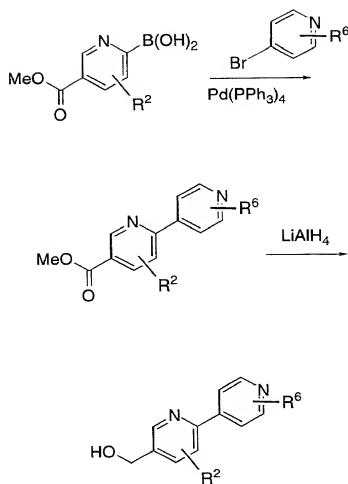
Scheme 78 illustrates the use of halogenated 2-amino-pyrimidine in the preparation of compounds of the instant invention.

SCHEME 67

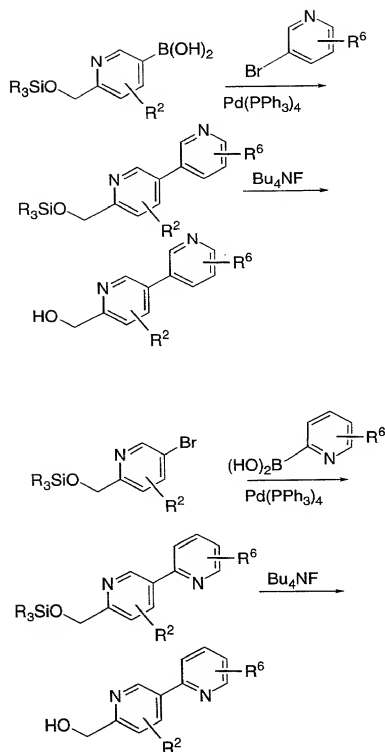


SCHEME 67 (continued)

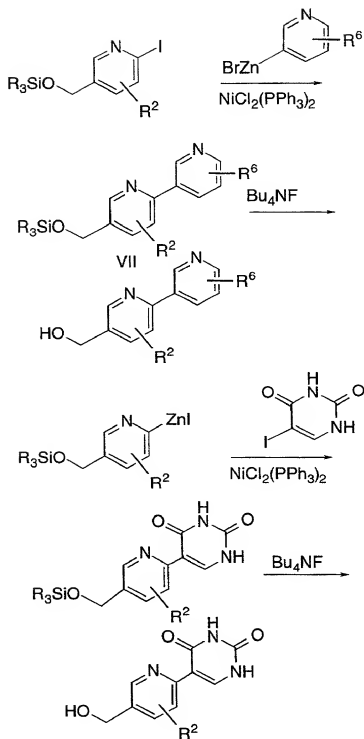
SCHEME 68

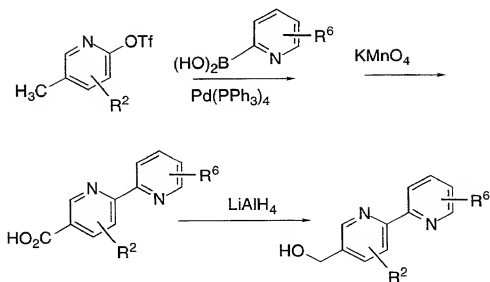


SCHEME 69

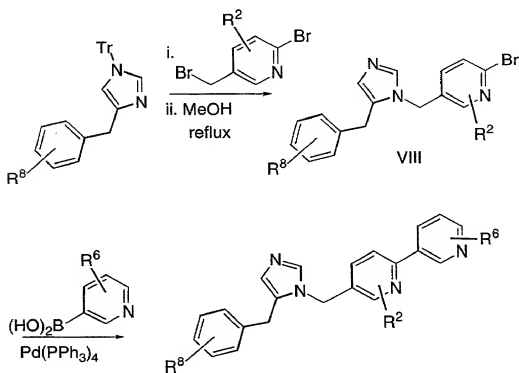


SCHEME 70

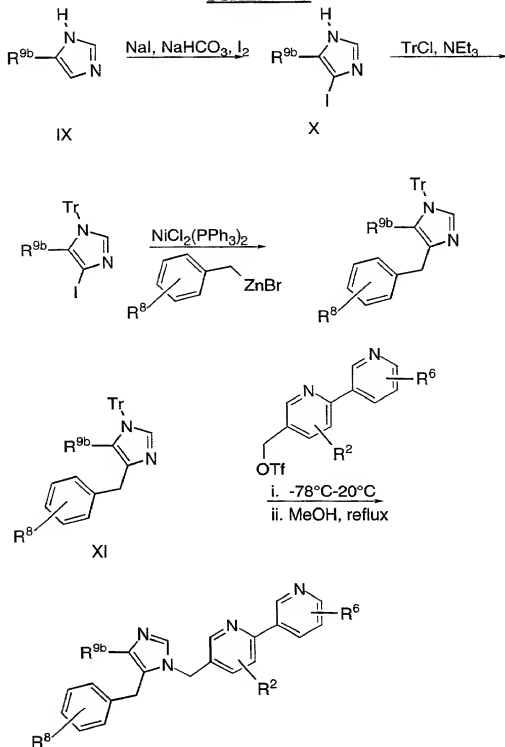


SCHEME 71

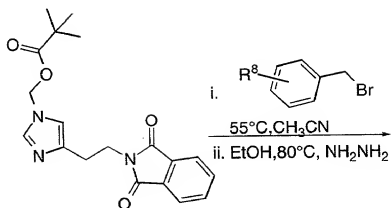
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SCHEME 72

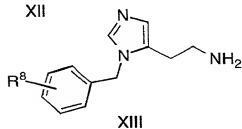
SCHEME 73



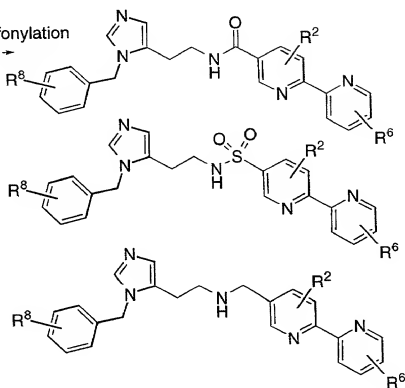
SCHEME 74



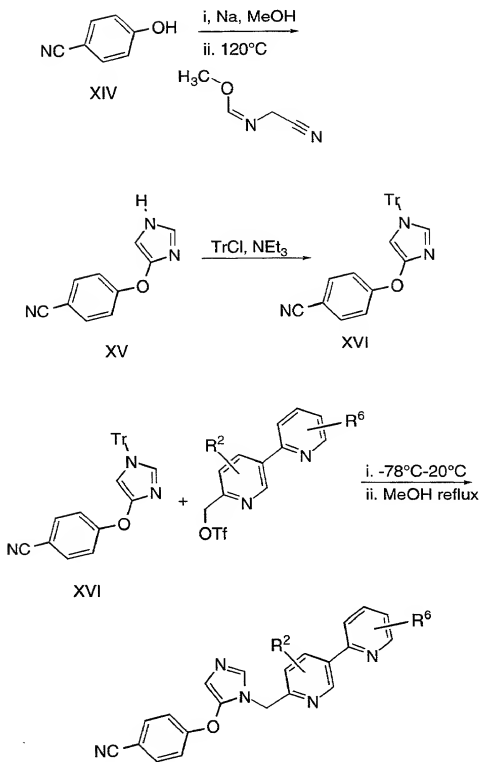
XII



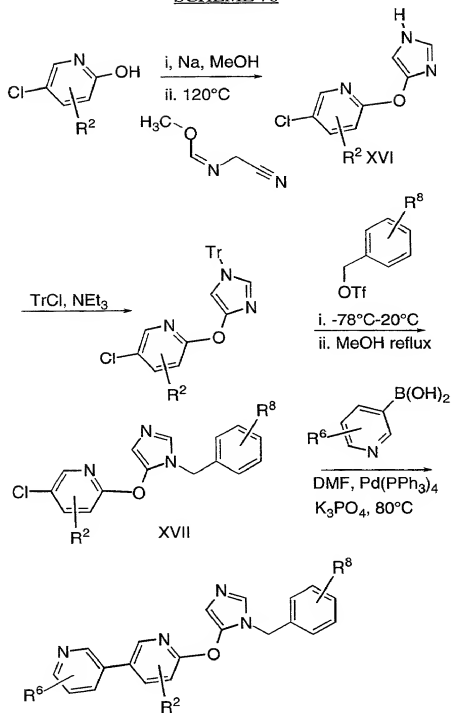
acylation, sulfonylation
or alkylation



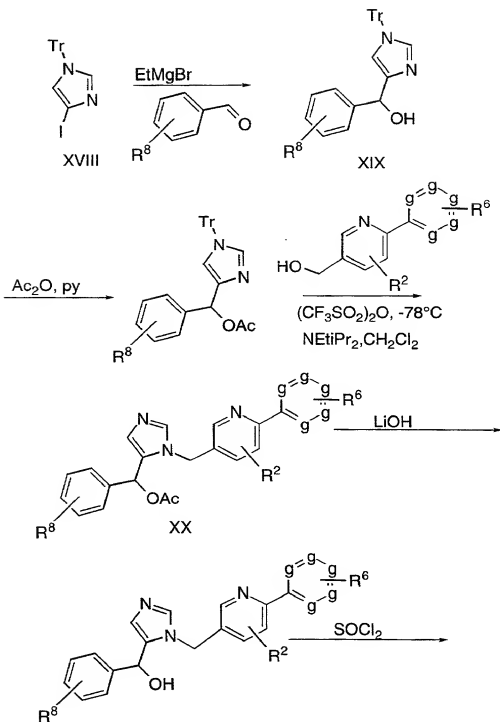
SCHEME 75

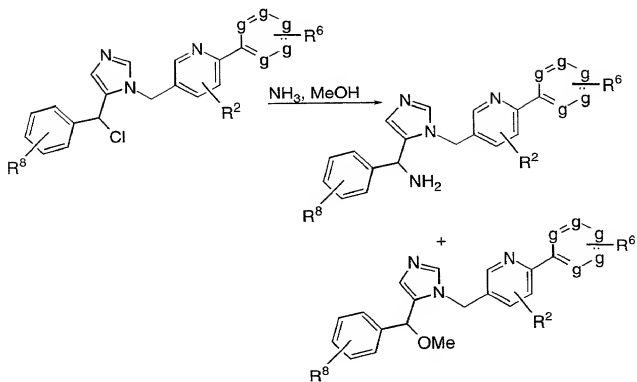
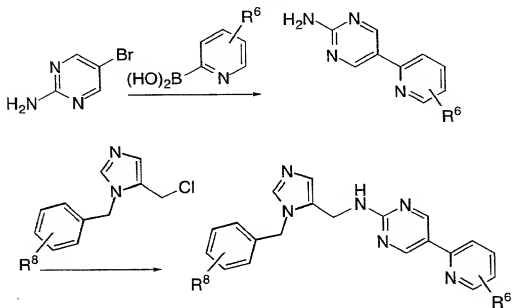


SCHEME 76



SCHEME 77



SCHEME 77 (continued)SCHEME 78

The farnesyl transferase inhibitors of formula (II-j) can be synthesized in accordance with Schemes 79-88, in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures. Substituents R³, R⁶ and R⁸, as shown in the Schemes, represent the substituents R³, R⁴, R⁵, R^{6a}, R^{6b}, R^{6c}, R^{6d}, R^{6e} and R⁸; although only one such R³, R⁶ or R⁸ is present in the intermediates and products of the schemes, it is understood that the reactions shown are also applicable when such aryl or heterocyclic moieties contain multiple substituents.

These reactions may be employed in a linear sequence to provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the alkylation reactions described in the Schemes. The reactions described in the Schemes are illustrative only and are not meant to be limiting. Other reactions useful in the preparation of heteroaryl moieties are described in "Comprehensive Organic Chemistry, Volume 4: Heterocyclic Compounds" ed. P.G. Sammes, Oxford (1979) and references therein.

Synopsis of Schemes 79-88:

The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures. Schemes 79-88 illustrate synthesis of the instant bicyclic compounds which incorporate a preferred benzylimidazolyl side chain. Thus, in Scheme 79, for example, a bicyclic intermediate that is not commercially available may be synthesized by methods known in the art. Thus, a suitably substituted pyridinone **1** may be reacted under coupling conditions with a suitably substituted iodobenzyl alcohol to provide the intermediate alcohol **2**. The intermediate alcohol **2** may be converted to the corresponding bromide **3**. The bromide **3** may be coupled to a suitably substituted benzylimidazolyl **4** to provide, after deprotection, the instant compound **5**.

Schemes 80-82 illustrate methods of synthesizing related or analogous key alcohol intermediates, which can then be processed as described in Scheme 79. Thus, Scheme 80 illustrates pyridinonyl-pyridyl alcohol forming reactions starting with the suitably

5 substituted iodonicotinate **6**.

Scheme 81 illustrates preparation of the intermediate alcohol **9** wherein the terminal lactam ring is saturated. Acylation of a suitably substituted 4-aminobenzyl alcohol **7** with a suitably substituted brominated acyl chloride provides the bisacylated
10 intermediate **8**. Closure of the lactam ring followed by saponification of the remaining acyl group provides the intermediate alcohol. Preparation of the homologous saturated lactam **10** is illustrated in Scheme 82.

Scheme 83 illustrates the synthesis of the alcohol
15 intermediate **13** which incorporates a terminal pyrazinone moiety. Thus, the amide of a suitably substituted amino acid **11** is formed and reacted with glyoxal to form the pyrazine **12**, which then undergoes the Ullmann coupling to form intermediate **13**.

Scheme 84 illustrates synthesis of an instant compound
20 wherein a non-hydrogen R^{9b} is incorporated in the instant compound. Thus, a readily available 4-substituted imidazole **14** may be selectively iodinated to provide the 5-iodoimidazole **15**. That imidazole may then be protected and coupled to a suitably substituted benzyl moiety to provide intermediate **16**. Intermediate **16** can then
25 undergo the alkylation reactions that were described hereinabove.

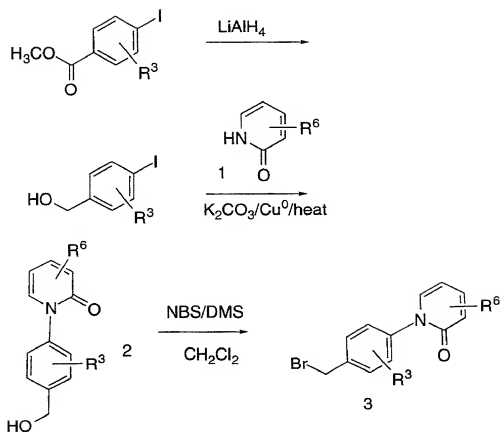
Scheme 85 illustrates synthesis of instant compounds that incorporate a preferred imidazolyl moiety connected to the bicyclic moiety via an alkyl amino, sulfonamide or amide linker. Thus, the 4-aminoalkylimidazole **17**, wherein the primary amine is protected
30 as the phthalimide, is selectively alkylated then deprotected to provide the amine **18**. The amine **18** may then react under conditions well known in the art with various activated bicyclic moieties to provide the instant compounds shown.

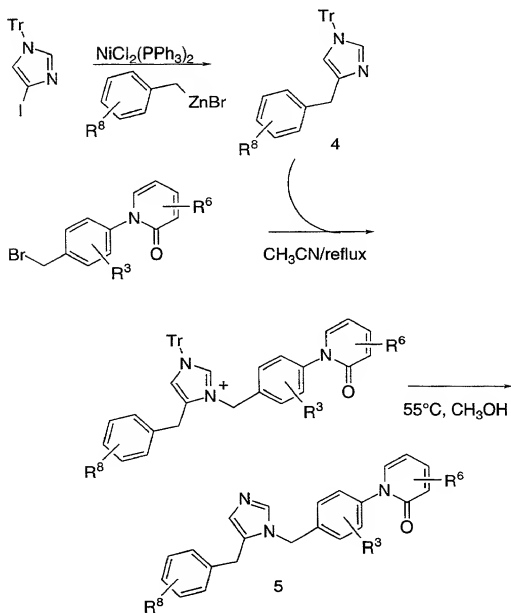
Compounds of the instant invention wherein the $A^1(CR^1_2)_nA^2(CR^1_2)_n$ linker is oxygen may be synthesized by methods known in the art, for example as shown in Scheme 86. The suitably substituted phenol **19** may be reacted with methyl

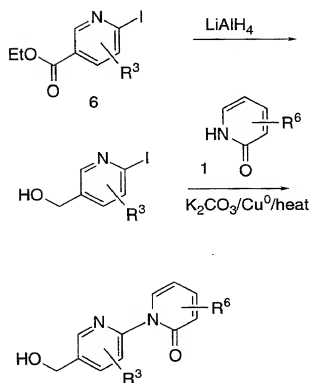
5 N-(cyano)methanimidate to provide the 4-phenoxyimidazole **20**. After selective protection of one of the imidazolyl nitrogens, the intermediate **21** can undergo alkylation reactions as described for the benzylimidazoles hereinabove.

- Compounds of the instant invention wherein the
- 10 $A^1(CR^1_2)_nA^2(CR^1_2)_n$ linker is a substituted methylene may be synthesized by the methods shown in Scheme 87. Thus, the N-protected imidazolyl iodide **22** is reacted, under Grignard conditions with a suitably protected benzaldehyde to provide the alcohol **23**. Acylation, followed by the alkylation procedure
- 15 illustrated in the Schemes above (in particular, Scheme 79) provides the instant compound **24**. If other R^1 substituents are desired, the acetyl moiety can be manipulated as illustrated in the Scheme.

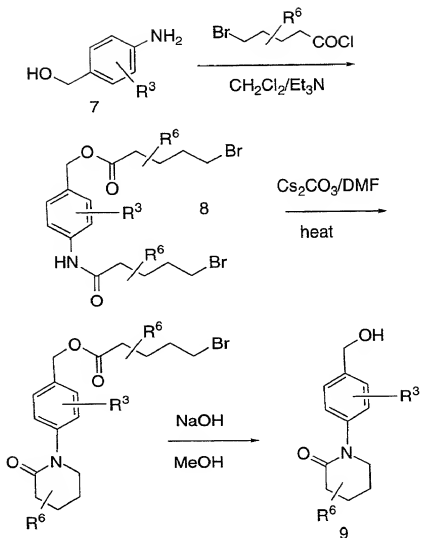
- Scheme 88 illustrates incorporation of an acetyl moiety as the $(CR^2_2)_pX(CR^2_2)_p$ linker of the instant compounds. Thus the
- 20 readily available methylphenone **25** undergoes the Ullmann reaction and the acetyl is brominated to provide intermediate **26**. Reaction with the imidazolyl reagent **4** provides, after deprotection, the instant compound **27**.

SCHEME 79

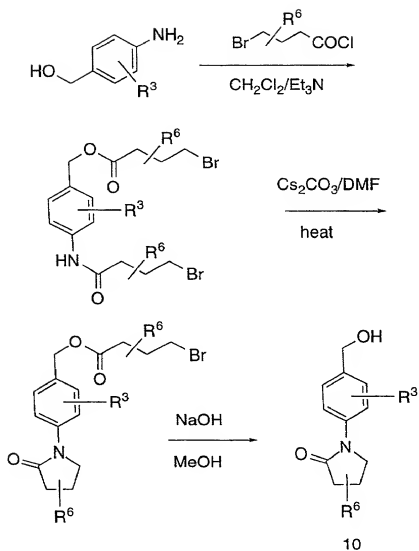
SCHEME 79 (continued)

SCHEME 80

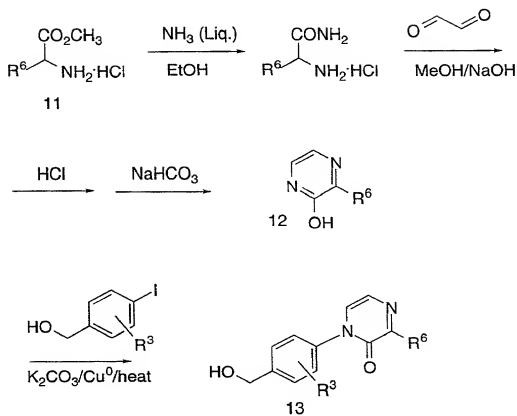
SCHEME 81



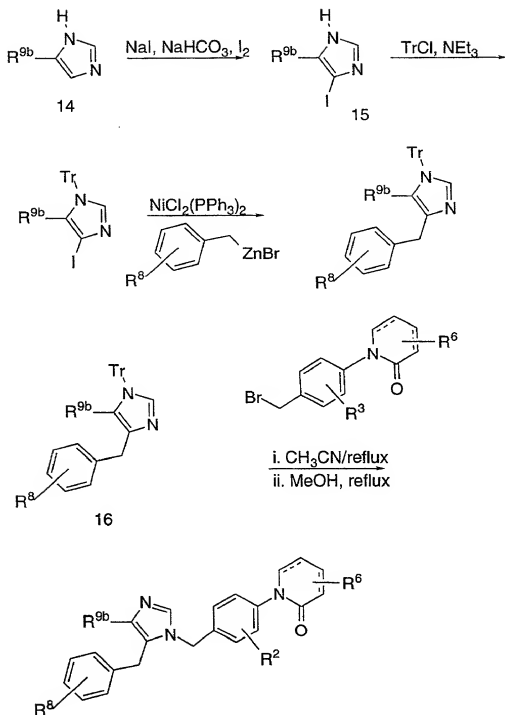
SCHEME 82



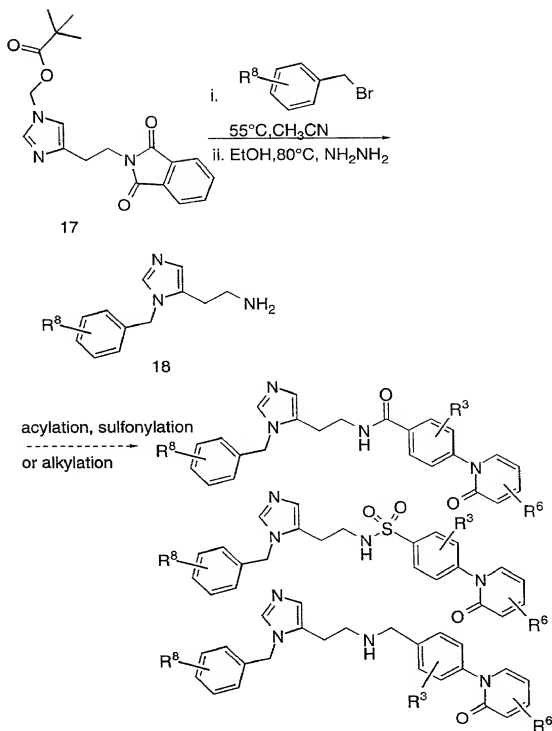
SCHEME 83



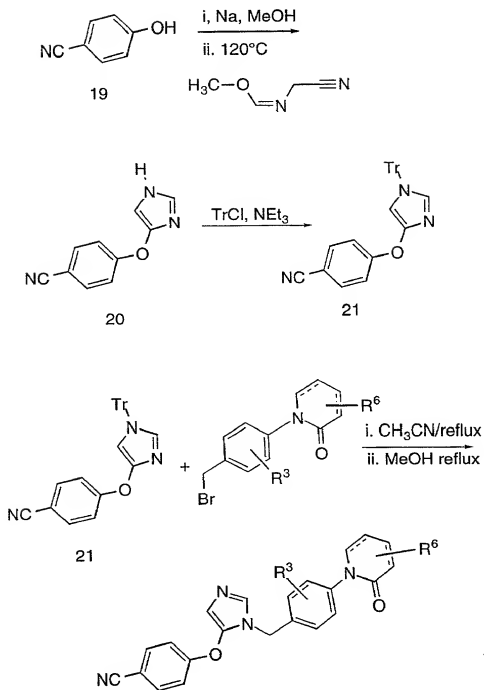
SCHEME 84



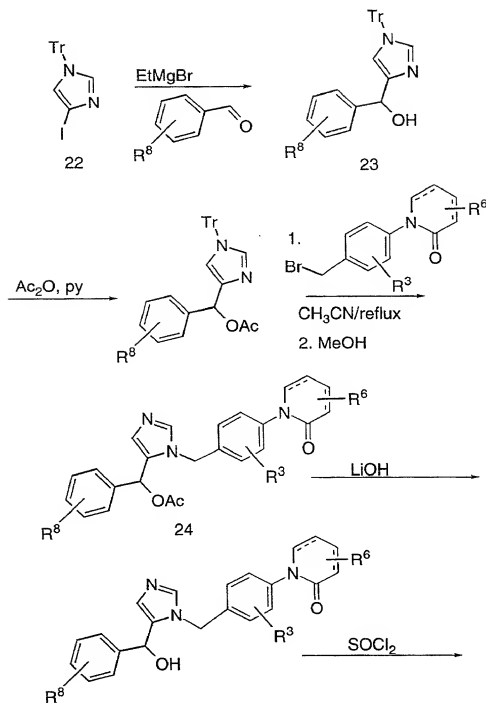
SCHEME 85

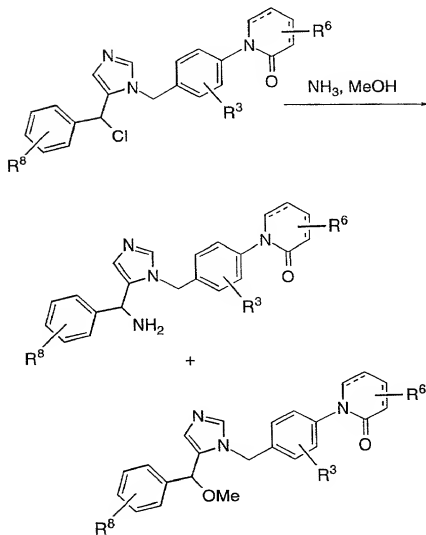


SCHEME 86

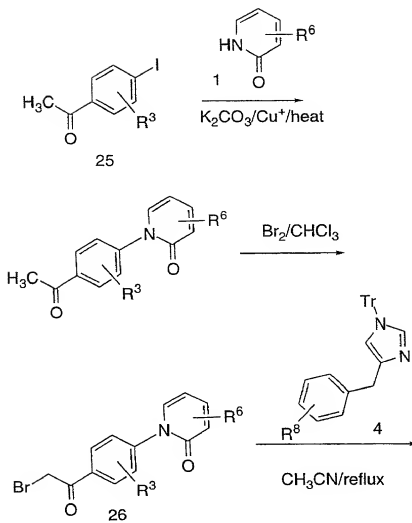


SCHEME 87

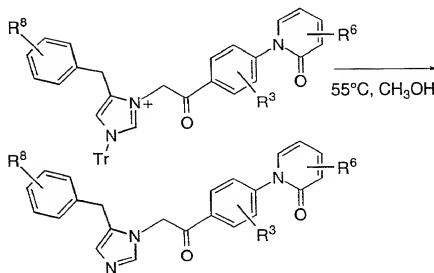


SCHEME 87 (continued)

SCHEME 88



SCHEME 88 (continued)



27

- 5 The farnesyl transferase inhibitors of formula (II-k) can be synthesized in accordance with Schemes 89-97, in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures. Substituents R^3 , R^6 and R^8 , as shown in the Schemes, represent the substituents R^3 , R^4 , R^5 , R^6a , R^6b , R^6c , R^6d , R^6e and R^8 ; although only one such R^3 , R^6 or R^8 is present in the intermediates and products of the schemes, it is understood that the reactions shown are also applicable when such aryl or heterocyclic moieties contain multiple substituents.
- 10
- 15 These reactions may be employed in a linear sequence to provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the alkylation reactions described in the Schemes. The reactions described in the Schemes are illustrative only and are not meant to be limiting. Other
- 20 reactions useful in the preparation of heteroaryl moieties are described in "Comprehensive Organic Chemistry, Volume 4:

Heterocyclic Compounds" ed. P.G. Sammes, Oxford (1979) and references therein.

Synopsis of Schemes 89-97:

5 The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures. Schemes 89-96 illustrate synthesis of the instant bicyclic compounds which incorporate a preferred benzylimidazolyl side-chain. Thus, in Scheme 89, for example, a bicyclic intermediate that
10 is not commercially available may be synthesized by methods known in the art. Thus, a suitably substituted pyridinonyl alcohol **29** may be synthesized starting from the corresponding isonicotinate **28** according to procedures described by Boekelhiede and Lehn (*J. Org. Chem.*, 26:428-430 (1961)). The alcohol is then protected and
15 reacted under Ullmann coupling conditions with a suitably substituted phenyl iodide, to provide the intermediate bicyclic alcohol **30**. The intermediate alcohol **30** may be converted to the corresponding bromide **31**. The bromide **31** may be coupled to a suitably substituted benzylimidazolyl **32** to provide, after deprotection,
20 the instant compound **33**.

Schemes 90-92 illustrate methods of synthesizing related or alcohol intermediates, which can then be processed as described in Scheme 89. Thus, Scheme 90 illustrates preparation of a pyridylpyridinonyl alcohol and thienylpyridinonyl alcohol starting with the
25 suitably substituted halogenated heterocycles.

Scheme 91 illustrates preparation of the intermediate bromide **36** wherein the preferred pyridinone is replaced by a saturated lactam. Acylation of a suitably substituted aniline **34** with a suitably substituted brominated acyl chloride provides the acylated
30 intermediate **35**. Closure of the lactam ring provides the intermediate alcohol, which is converted to the bromide as described above.

Scheme 92 illustrates synthesis of an instant

compound wherein a non-hydrogen R^{9b} is incorporated in the instant compound. Thus, a readily available 4-substituted imidazole **37** may be selectively iodinated to provide the 5-iodoimidazole **38**. That imidazole **38** may then be protected and coupled to a suitably substituted benzyl moiety to provide intermediate **39**. Intermediate **39** can then undergo the alkylation reactions that were described hereinabove.

Scheme 93 illustrates synthesis of instant compounds that incorporate a preferred imidazolyl moiety connected to the biaryl via an alkyl amino, sulfonamide or amide linker. Thus, the 4-aminoalkylimidazole **40**, wherein the primary amine is protected as the phthalimide, is selectively alkylated then deprotected to provide the amine **41**. The amine **41** may then react under conditions well known in the art with various activated arylheteroaryl moieties to provide the instant compounds shown.

Compounds of the instant invention wherein the $A^1(CR^1_2)_nA^2(CR^1_2)_n$ linker is oxygen may be synthesized by methods known in the art, for example as shown in Scheme 94. The suitably substituted phenol **42** may be reacted with methyl N-(cyano)methanimidate to provide the 4-phenoxyimidazole **43**. After selective protection of one of the imidazolyl nitrogens, the intermediate **44** can undergo alkylation reactions as described for the benzylimidazoles hereinabove.

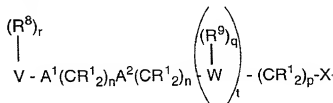
Compounds of the instant invention wherein the $A^1(CR^1_2)_nA^2(CR^1_2)_n$ linker is a substituted methylene may be synthesized by the methods shown in Scheme 95. Thus, the N-protected imidazolyl iodide **45** is reacted, under Grignard conditions with a suitably protected benzaldehyde to provide the alcohol **46**. Acylation, followed by the alkylation procedure illustrated in the Schemes above (in particular, Scheme 89) provides the instant compound **47**. If other R^1 substituents are desired, the acetyl moiety can be manipulated as illustrated in the Scheme.

Scheme 96 illustrates incorporation of an acetyl

moiety as the $(CR^2_2)_pX(CR^2_2)_p$ linker of the instant compounds.

Thus, the suitably substituted acetyl pyridine **48** is converted to the corresponding pyridinone and undergoes the Ullmann reaction with a suitably substituted phenyl iodide. The acetyl is then brominated to provide intermediate **49**. Reaction with the imidazolyl reagent **32** provides, after deprotection, the instant compound **50**.

Scheme 97 illustrate reactions wherein the moiety



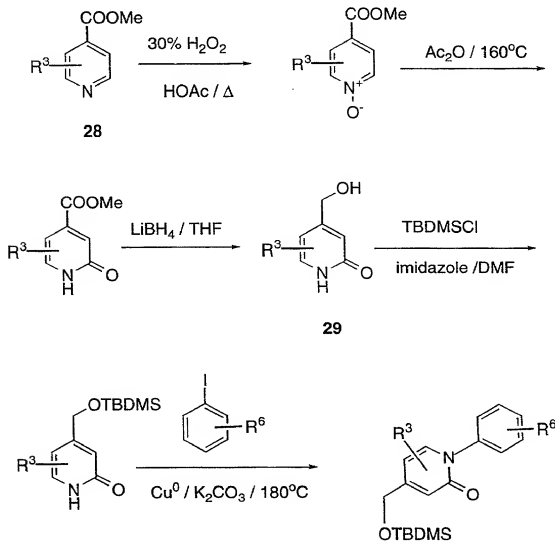
incorporated in the compounds of the instant invention is represented by other than a substituted imidazole-containing group.

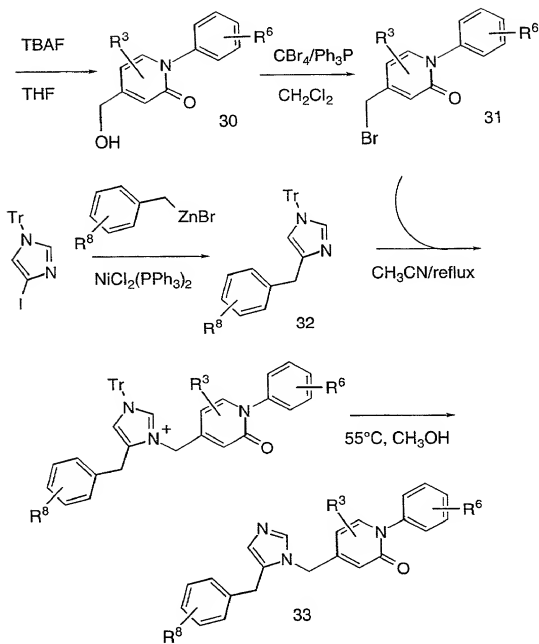
Thus, the intermediates whose synthesis are illustrated in the Schemes, and other pyridinonecarbocyclic and pyridinoneheterocyclic intermediates obtained commercially or readily synthesized, can be coupled with a variety of aldehydes. The aldehydes can be prepared by standard procedures, such as that described by O. P. Goel, U. Krolls, M. Stier and S. Kesten in Organic Syntheses, **1988**, 67, 69-75, from the appropriate amino acid. Knochel chemistry may be utilized, as shown in Scheme 97, to incorporate the arylpyridinone moiety. Thus, a suitably substituted 4-(bromo)-pyridine is converted to the corresponding pyridinone **51** as described above and the pyridinone is coupled to a suitably substituted phenyl iodide as previously described above. The resulting bromide **52** is treated with zinc(0) and the resulting zinc bromide reagent **53** is reacted with an aldehyde to provide the C-alkylated instant compound **54**. Compound **54** can be deoxygenated by methods known in the art, such as a catalytic hydrogenation, then deprotected with trifluoroacetic acid in methylene chloride to give the final compound **55**. The compound **55** may be isolated in the salt form, for example, as a trifluoroacetate, hydrochloride or acetate salt, among others. The product diamine **55** can further be

selectively protected to obtain **56**, which can subsequently be reductively alkylated with a second aldehyde to obtain compound **57**. Removal of the protecting group, and conversion to cyclized products such as the dihydroimidazole **58** can be accomplished by

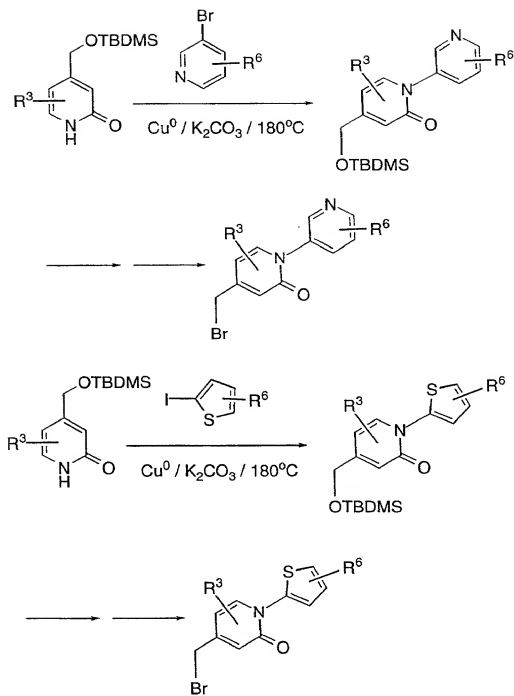
5 literature procedures.

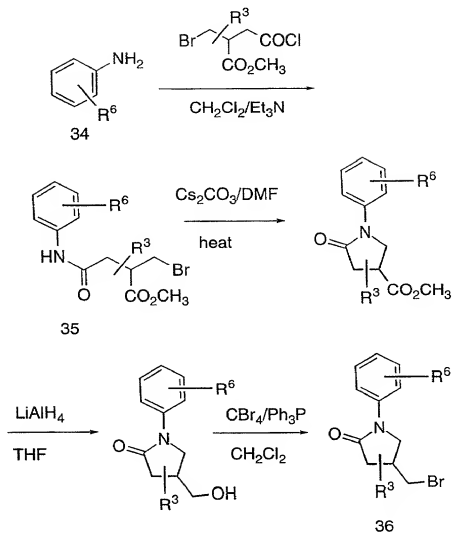
SCHEME 89



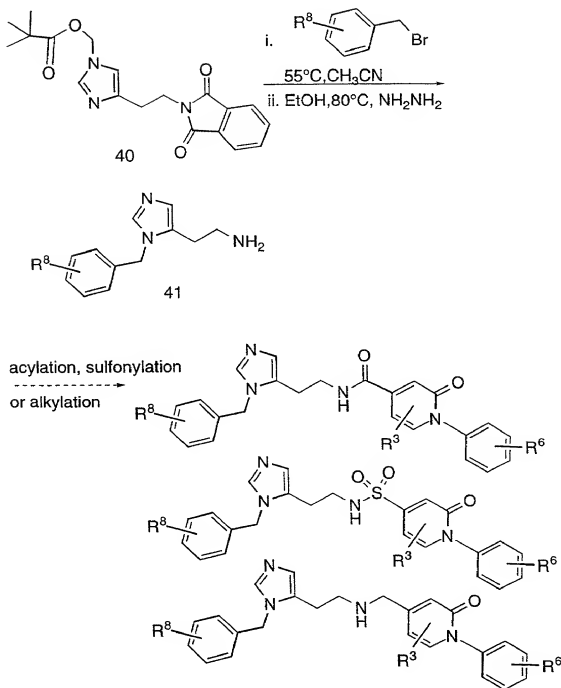
SCHEME 89 (continued)

SCHEME 90

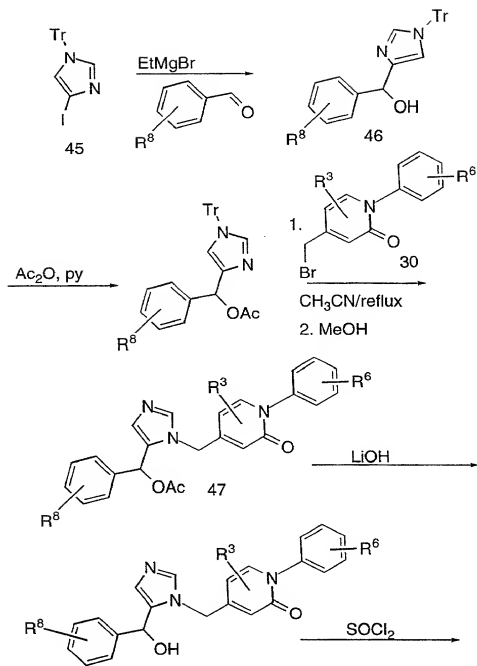


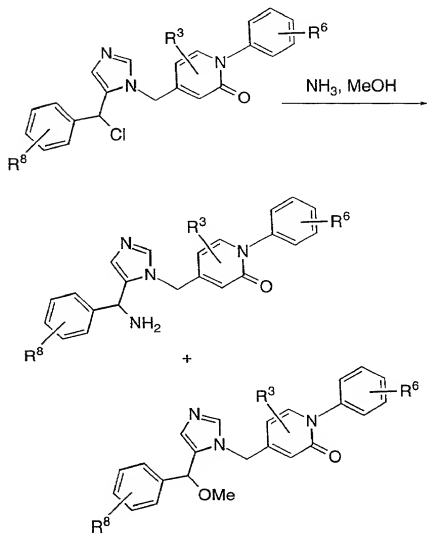
SCHEME 91

SCHEME 93

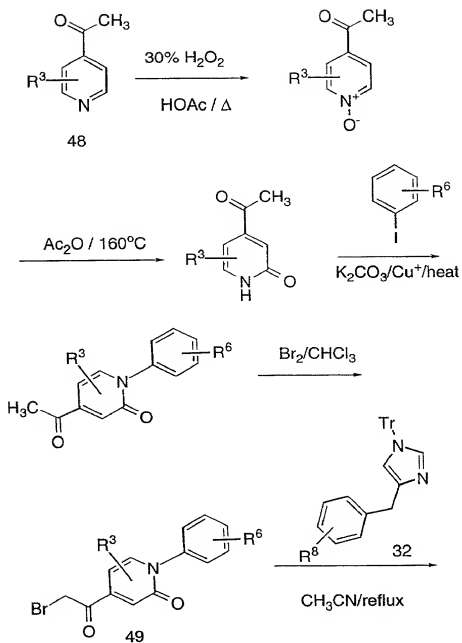


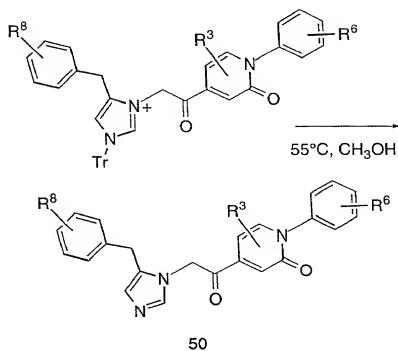
SCHEME 95



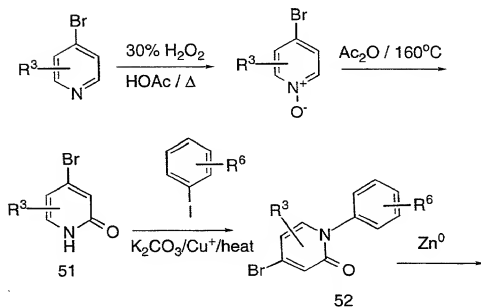
SCHEME 95 (continued)

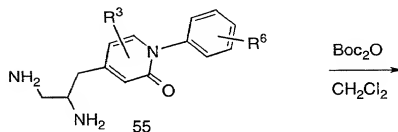
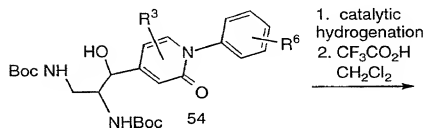
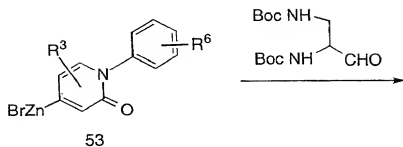
SCHEME 96

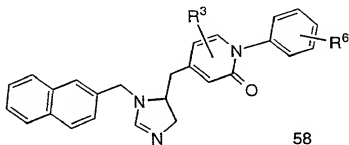
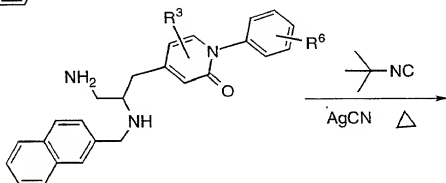
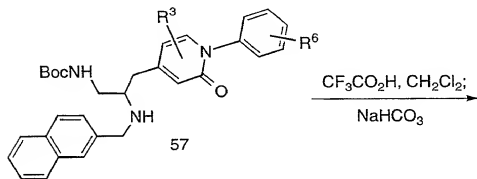
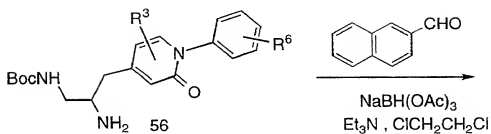


SCHEME 96 (continued)

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SCHEME 97

SCHEME 97 (continued)

SCHEME 97 (continued)

The farnesyl transferase inhibitors of formula (II-i) can be synthesized in accordance with Reaction Schemes, in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures. Some key reactions utilized to form the aminodiphenyl moiety of the instant compounds are shown.

These reactions may be employed in a linear sequence to provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the alkylation reactions described in the Reaction Schemes.

Reaction Schemes A-P describe the preparation of appropriately substituted aniline intermediates that may be further functionalized by the methods described in Reaction Schemes Q-Y to provide the compounds of the instant invention.

Reaction Schemes A-D illustrate use of Ullman reactions to provide diphenyl ethers, amines and sulfides from readily available fully substituted phenols/thiophenols/anilines and aryl halides. In such syntheses, the desired amine moiety is typically masked as a nitro group which is subsequently reduced by techniques well known in the art. An alternative synthesis of the diphenyl ethers which employs para-nitro fluorobenzene is shown in Reaction Scheme E.

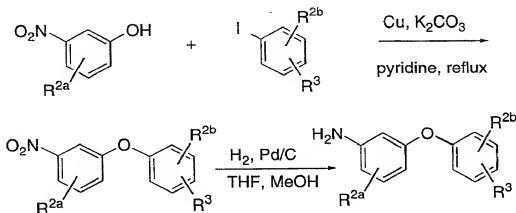
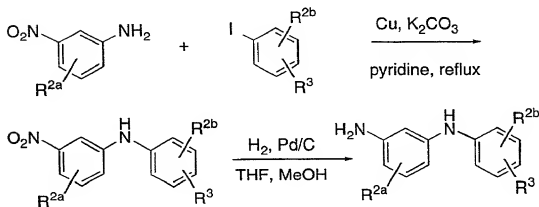
Reaction Scheme F illustrates standard acid-amine coupling to provide the fully substituted N-phenylbenzamides. Reaction Scheme G illustrates formation of the aminomethyl spacer via a reductive amination of a suitably substituted benzaldehyde.

Reaction Scheme H illustrates coupling of suitably substituted anilines with readily available phenylsulfonyl chlorides. Access to aminobenzophenones is illustrated in Reaction Scheme I, which also illustrates the reduction of the carbonyl to provide the unsubstituted methyl spacer. An alternative method of forming the benzophenone intermediates is illustrated in Reaction Scheme J. Also shown in Reaction Scheme J is reductive amination of the resulting carbonyl to provide the amine substituted methyl spacer. Another

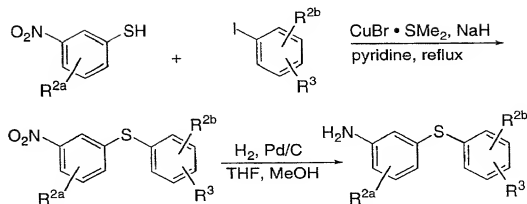
method of forming the benzophenone intermediates, illustrated in Reaction Scheme K, is a Stille reaction with an aryl stannane.

- Reaction Schemes L and M illustrate palladium mediated formation of olefin and acetylene spacer units. Reaction Scheme N illustrates formation of an appropriately substituted benzyl ether. Reaction Scheme P illustrates the use of the Claisen rearrangement to provide methyl spacers having substituents such as a vinyl group which can be further functionalized.

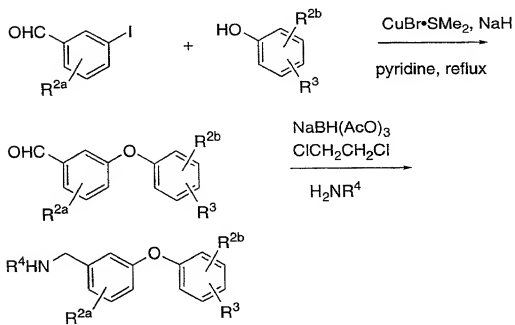
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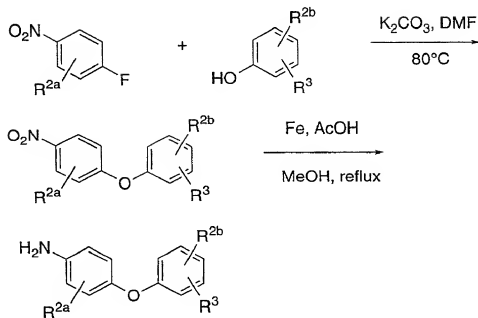
REACTION SCHEME AREACTION SCHEME B

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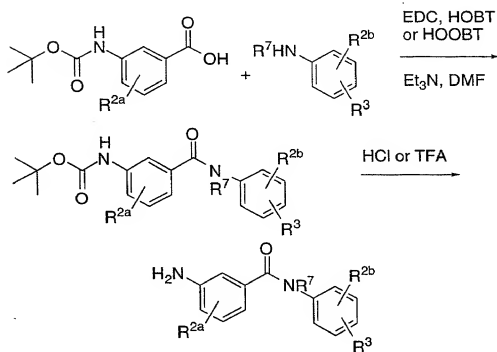
REACTION SCHEME C

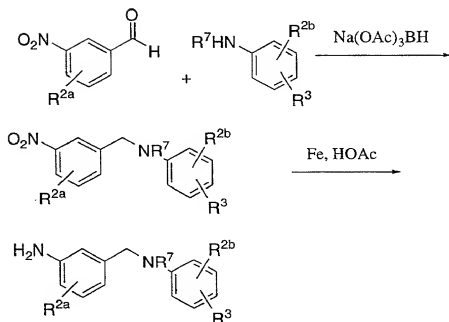
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REACTION SCHEME D

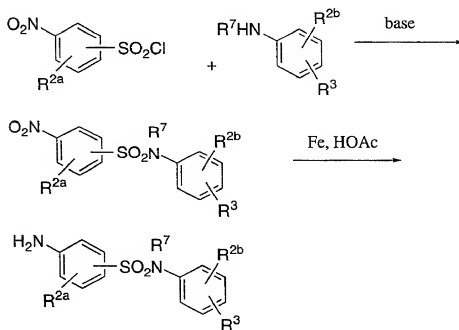
REACTION SCHEME E

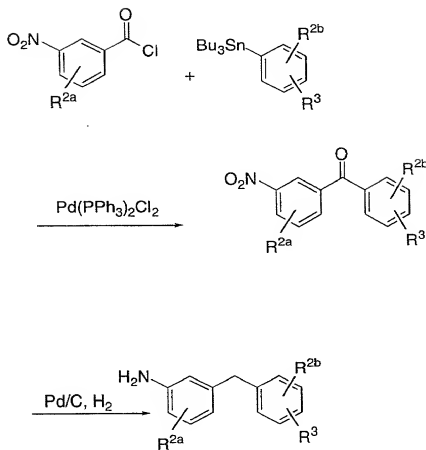
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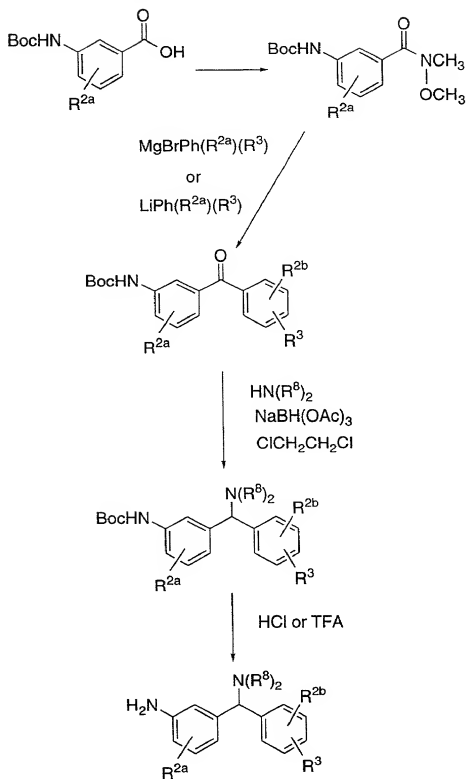
REACTION SCHEME F

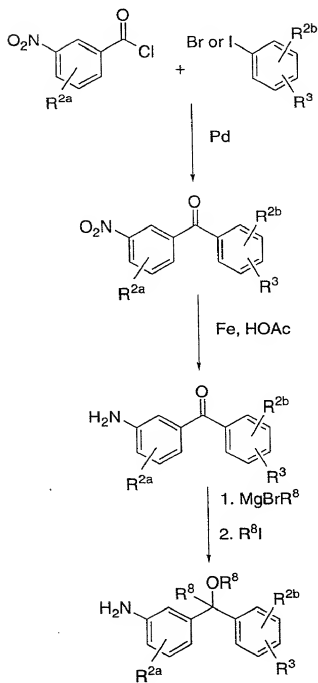
REACTION SCHEME GREACTION SCHEME H

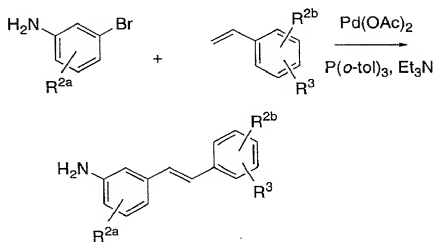
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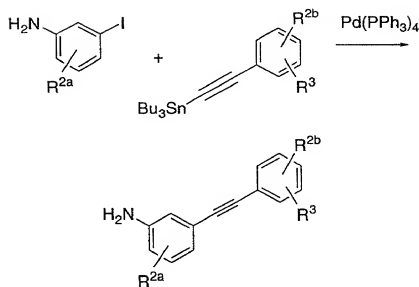
REACTION SCHEME I

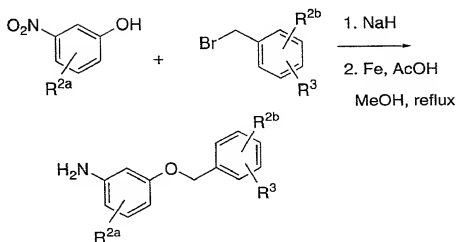
REACTION SCHEME I

REACTION SCHEME K

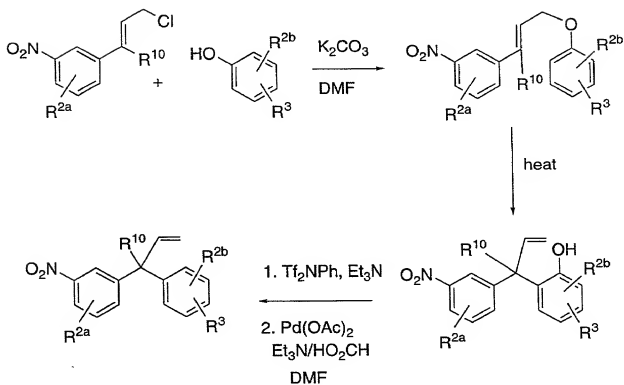
REACTION SCHEME L

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REACTION SCHEME M

REACTION SCHEME N

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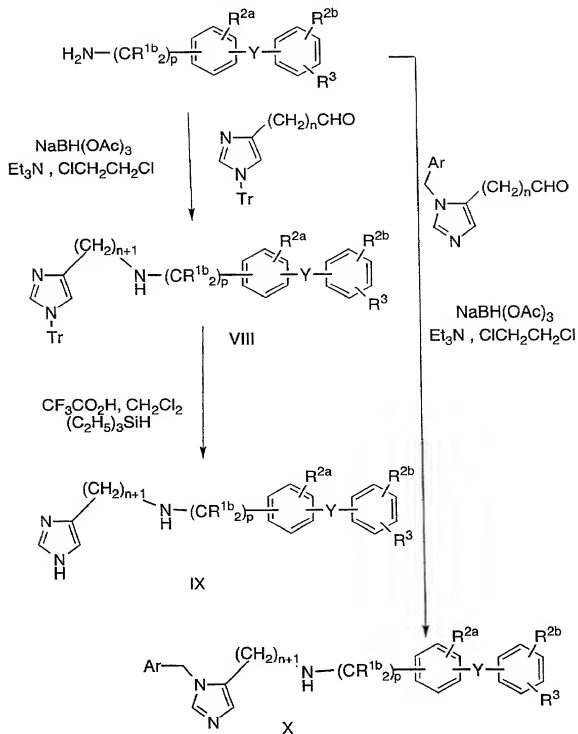
REACTION SCHEME P

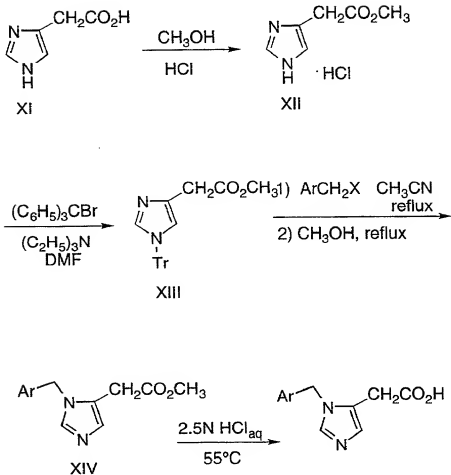
Reaction Schemes Q- S illustrate reactions wherein the non-sulphydryl-containing moiety(ies) of the compounds of the instant invention is attached to the aminodiphenyl subunit to provide the instant compounds.

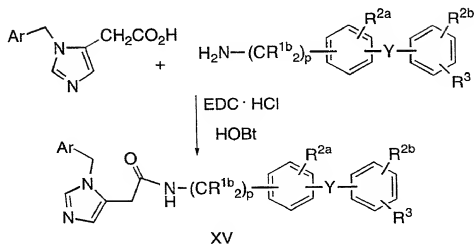
- 5 Thus, the aminodiphenyl subunit can be reductively alkylated with aldehydes such as 1-trityl-4-carboxaldehyde or 1-trityl-4-imidazolylacetaldehyde, to give products such as **VIII** (Reaction Scheme Q). The trityl protecting group can be removed from **VIII** to give **IX**, or alternatively, **VIII** can first be treated with an alkyl
10 halide then subsequently deprotected to give the alkylated imidazole **X**. Alternatively, the aminomethylbenzamide subunit can be acylated or sulfonylated by standard techniques.

- The imidazole acetic acid **XI** can be converted to the acetate **XIII** by standard procedures, and **XIII** can be first reacted
15 with an alkyl halide, then treated with refluxing methanol to provide the regiospecifically alkylated imidazole acetic acid ester **XIV**. Hydrolysis and reaction with the aminodiphenyl subunit in the presence of condensing reagents such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) leads to acylated products such as **XV**.
20 Coupling reactions with other suitably substituted aldehydes may be performed as illustrated in Schemes 3 and 6-9 hereinabove.

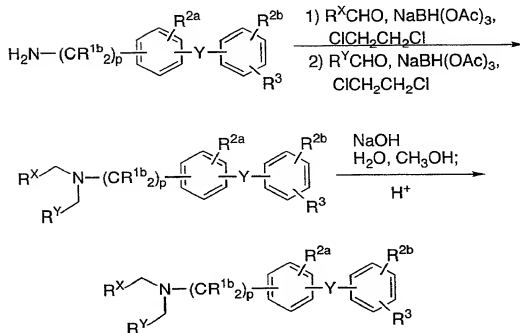
- Reaction Scheme S illustrates a one pot synthesis of an instant compound wherein the N-terminus nitrogen is substituted with two different non-sulphydryl-containing moieties. Thus, the
25 aminodiphenyl subunit is treated with one equivalent of an appropriate aldehyde and, after the reductive adduct has been formed, the in situ intermediate is treated with an equivalent of a different aldehyde.

REACTION SCHEME Q

REACTION SCHEME R

REACTION SCHEME R (continued)

5

REACTION SCHEME S

- 10 wherein, in the above Reaction Schemes, R' is R^{1a}; R'' is (R⁶)_{F-V-A1}-(CR^{1a})_n-; R''' is selected such that R'''CH₂- is R⁸; and R^x and R^y are selected such that R^xCH₂- and R^yCH₂- are either R⁴ or R⁵.

EXAMPLES

- Examples provided are intended to assist in a further understanding of the invention. Particular materials employed, species and conditions are intended to be further illustrative of the invention and not limitative of the reasonable scope thereof.

- The standard workup referred to in the examples refers to solvent extraction and washing the organic solution with 10% citric acid, 10% sodium bicarbonate and brine as appropriate. Solutions were dried over sodium sulfate and evaporated in vacuo on a rotary evaporator.

EXAMPLE 1

- (S)-1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)-imidazolylmethyl]-5-[2-(methanesulfonyl)ethyl]-2-piperazinone dihydrochloride

Step A: 1-triphenylmethyl-4-(hydroxymethyl)-imidazole

- To a solution of 4-(hydroxymethyl)imidazole hydrochloride (35.0 g, 260 mmol) in 250 mL of dry DMF at room temperature was added triethylamine (90.6 mL, 650 mmol). A white solid precipitated from the solution. Chlorotriphenylmethane (76.1 g, 273 mmol) in 500 mL of DMF was added dropwise. The reaction mixture was stirred for 20 hours, poured over ice, filtered, and washed with ice water. The resulting product was slurried with cold dioxane, filtered, and dried *in vacuo* to provide the titled product as a white solid which was sufficiently pure for use in the next step.

Step B: 1-triphenylmethyl-4-(acetoxymethyl)-imidazole

- Alcohol from Step A (260 mmol, prepared above) was suspended in 500 mL of pyridine. Acetic anhydride (74 mL, 780 mmol) was added dropwise, and the reaction was stirred for 48 hours during which it became homogeneous. The solution was poured into 2 L of EtOAc, washed with water (3 x 1 L), 5% aq. HCl soln. (2 x 1 L), sat. aq. NaHCO₃, and brine, then dried (Na₂SO₄), filtered, and

concentrated *in vacuo* to provide the crude product. The acetate was isolated as a white powder which was sufficiently pure for use in the next reaction.

5 Step C: 1-(4-cyanobenzyl)-5-(acetoxymethyl)-imidazole
 hydrobromide

 A solution of the product from Step B (85.8 g, 225 mmol) and α -bromo-*p*-tolunitrile (50.1 g, 232 mmol) in 500 mL of EtOAc was stirred at 60°C for 20 hours, during which a pale yellow precipitate
10 formed. The reaction was cooled to room temperature and filtered to provide the solid imidazolium bromide salt. The filtrate was concentrated *in vacuo* to a volume 200 mL, reheated at 60°C for two hours, cooled to room temperature, and filtered again. The filtrate was concentrated *in vacuo* to a volume 100 mL, reheated at 60°C for another
15 two hours, cooled to room temperature, and concentrated *in vacuo* to provide a pale yellow solid. All of the solid material was combined, dissolved in 500 mL of methanol, and warmed to 60°C. After two hours, the solution was reconcentrated *in vacuo* to provide a white solid which was triturated with hexane to remove soluble materials. Removal
20 of residual solvents *in vacuo* provided the titled product hydrobromide as a white solid which was used in the next step without further purification.

25 Step D: 1-(4-cyanobenzyl)-5-(hydroxymethyl)-imidazole

 To a solution of the acetate from Step C (50.4 g, 150 mmol) in 1.5 L of 3:1 THF/water at 0 °C was added lithium hydroxide monohydrate (18.9 g, 450 mmol). After one hour, the reaction was concentrated *in vacuo*, diluted with EtOAc (3 L), and washed with water, sat. aq. NaHCO₃ and brine. The solution was then dried
30 (Na₂SO₄), filtered, and concentrated *in vacuo* to provide the crude product as a pale yellow fluffy solid which was sufficiently pure for use in the next step without further purification.

Step E: 1-(4-cyanobenzyl)-5-imidazolecarboxaldehyde

To a solution of the alcohol from Step D (21.5 g, 101 mmol) in 500 mL of DMSO at room temperature was added triethylamine (56 mL, 402 mmol), then SO₃-pyridine complex (40.5 g, 254 mmol). After 45 minutes, the reaction was poured into 2.5 L of EtOAc, washed with water (4 x 1 L) and brine, dried (Na₂SO₄), filtered, and concentrated *in vacuo* to provide the aldehyde as a white powder which was sufficiently pure for use in the next step without further purification.

Step F: (S)-2-(tert-butoxycarbonylamino)-N-methoxy-N-methyl-4-(methylthio)butanamide

L-N-Boc-methionine (30.0 g, 0.120 mol), *N,O*-dimethylhydroxylamine hydrochloride (14.1 g, 0.144 mol), EDC hydrochloride (27.7 g, 0.144 mol) and HOBt (19.5 g, 0.144 mol) were stirred in dry DMF (300 mL) at 20°C under nitrogen. More *N,O*-dimethylhydroxylamine hydrochloride (2.3 g, 23 mmol) was added to obtain pH 7-8. The reaction was stirred overnight, the DMF distilled to half the original volume under high vacuum, and the residue partitioned between ethyl acetate and sat. NaHCO₃ soln. The organic phase was washed with saturated sodium bicarbonate, water, 10% citric acid, and brine, and dried with sodium sulfate. The solvent was removed *in vacuo* to give the title compound.

Step G: (S)-2-(tert-butoxycarbonylamino)-4-(methylthio)butanal

A suspension of lithium aluminum hydride (5.02 g, 0.132 mol) in ether (500 mL) was stirred at room temperature for one hour. The solution was cooled to -50°C under nitrogen, and a solution of the product from Step F (39.8 g, ca. 0.120 mol) in ether (200 mL) was added over 30 min, maintaining the temperature below -40°C. When the addition was complete, the reaction was warmed to 5°C, then recooled to -45°C. Analysis by tlc revealed incomplete reaction. The solution was rewarmed to 5 °C, stirred for 30 minutes, then cooled to

-50°C. A solution of potassium hydrogen sulfate (72 g, 0.529 mol) in 200 mL water was slowly added, maintaining the temperature below -20°C. The mixture was warmed to 5°C, filtered through Celite, and concentrated *in vacuo* to provide the title aldehyde.

5

Step H: (S)-2-(tert-butoxycarbonylamino)-N-(3-chlorophenyl)-4-(methylthio)butanamine

To a solution of 3-chloroaniline (10.3 mL, 97.4 mmol), the product from Step G (23.9 g, 97.4 mmol), and acetic acid (27.8 mL, 487 mmol) in dichloroethane (250 mL) under nitrogen was added sodium triacetoxymethylborohydride (41.3 g, 195 mmol). The reaction was stirred overnight, then quenched with saturated sodium bicarbonate solution. The solution was diluted with CHCl₃, and the organic phase was washed with water, 10% citric acid and brine. The solution was dried over sodium sulfate and concentrated *in vacuo* to provide the crude product (34.8 g) which was chromatographed on silica gel with 20% ethyl acetate in hexane to obtain the title compound.

Step I: (S)-4-(tert-butoxycarbonyl)-1-(3-chlorophenyl)-5-[2-(methylthio)ethyl]piperazin-2-one

A solution of the product from Step H (22.0 g, 63.8 mmol) in ethyl acetate (150 mL) was vigorously stirred at 0°C with saturated sodium bicarbonate (150 mL). Chloroacetyl chloride (5.6 mL, 70.2 mmol) was added dropwise, and the reaction stirred at 0°C for 2h. The layers were separated, and the ethyl acetate phase was washed with 10% citric acid and saturated brine, and dried over sodium sulfate. After concentration *in vacuo*, the resulting crude product (27.6 g) was dissolved in DMF (300 mL) and cooled to 0°C under argon. Cesium carbonate (63.9 g, 196 mmol) was added, and the reaction was stirred for two days, allowing it to warm to room temperature. Another portion of cesium carbonate (10 g, 30 mmol) was added, and the reaction was stirred for 16 hours. The DMF was distilled *in vacuo*, and the residue partitioned between ethyl acetate and water. The organic phase was washed with saturated brine, and dried over sodium sulfate.

The crude product was chromatographed on silica gel with 20-25% ethyl acetate in hexane to obtain the title compound.

Step J: (S)-4-(*tert*-butoxycarbonyl)-1-(3-chlorophenyl)-5-[2-(methanesulfonyl)ethyl]piperazin-2-one

A solution of the product from Step I (14.2 g, 37 mmol) in methanol (300 mL) was cooled to 0°C, and a solution of magnesium monoperoxyphthalate (54.9 g, 111 mmol) in 210 mL MeOH was added over 20 minutes. The ice bath was removed, and the solution was allowed to warm to room temperature. After 45 minutes, the reaction was concentrated *in vacuo* to half the original volume, then quenched by the addition of 2N Na₂S₂O₃ soln. The solution was poured into EtOAc and sat NaHCO₃ solution, and the organic layer was washed with brine, dried (Na₂SO₄), filtered, and concentrated *in vacuo* to provide the crude sulfone. This material was chromatographed on silica gel with 60-100% ethyl acetate in hexane to obtain the titled compound.

Step K: (S)-1-(3-chlorophenyl)-5-[2-(methanesulfonyl)ethyl]piperazin-2-one

Through a solution of Boc-protected piperazinone from Step J (1.39 g, 3.33 mmol) in 30 mL of EtOAc at 0°C was bubbled anhydrous HCl gas. The saturated solution was stirred for 35 minutes, then concentrated *in vacuo* to provide the hydrochloride salt as a white powder. This material was suspended in EtOAc and treated with dilute aqueous NaHCO₃ solution. The aqueous phase was extracted with EtOAc, and the combined organic mixture was washed with brine, dried (Na₂SO₄), filtered, and concentrated *in vacuo*. The resulting amine was reconcentrated from toluene to provide the titled material suitable for use in the next step.

Step L: (S)-1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)imidazolyl-methyl]-5-[2-(methanesulfonyl)-ethyl]-2-piperazinone dihydrochloride

- To a solution of the amine from Step K (898 mg, 2.83 mmol) and imidazole carboxaldehyde from Step E (897 mg, 4.25 mmol) in 15 mL of 1,2-dichloroethane was added sodium triacetoxymethylborohydride (1.21 g, 5.7 mmol). The reaction was stirred for 23 hours, then quenched at 0°C with sat. NaHCO₃ solution. The solution was poured into CHCl₃, and the aqueous layer was back-extracted with CHCl₃. The combined organics were washed with brine, dried (Na₂SO₄), filtered, and concentrated *in vacuo*. The resulting product was purified by silica gel chromatography (95:5:0.5-90:10:0 EtOAc:MeOH:NH₄Cl), and the resultant product was taken up in EtOAc/methanol and treated with 2.1 equivalents of 1 M HCl/ether solution. After concentrated *in vacuo*, the product dihydrochloride was isolated as a white powder.

EXAMPLE 2

- 1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)imidazolyl-methyl]-2-piperazinone dihydrochloride

Step A: N-(3-chlorophenyl)ethylenediamine hydrochloride

- To a solution of 3-chloroaniline (30.0 mL, 284 mmol) in 500 mL of dichloromethane at 0°C was added dropwise a solution of 4 N HCl in 1,4-dioxane (80 mL, 320 mmol HCl). The solution was warmed to room temperature, then concentrated to dryness *in vacuo* to provide a white powder. A mixture of this powder with 2-oxazolidinone (24.6 g, 282 mmol) was heated under nitrogen atmosphere at 160°C for 10 hours, during which the solids melted, and gas evolution was observed. The reaction was allowed to cool, forming the crude diamine hydrochloride salt as a pale brown solid.

Step B: *N*-(*tert*-butoxycarbonyl)-*N'*-(3-chlorophenyl)ethylenediamine

- The amine hydrochloride from Step A (*ca.* 282 mmol, crude material prepared above) was taken up in 500 mL of THF and 500 mL of sat. aq. NaHCO₃ soln., cooled to 0°C, and di-*tert*-butylpyrocarbonate (61.6 g, 282 mmol) was added. After 30 h, the reaction was poured into EtOAc, washed with water and brine, dried (Na₂SO₄), filtered, and concentrated *in vacuo* to provide the titled carbamate as a brown oil which was used in the next step without further purification.

Step C: *N*-[2-(*tert*-butoxycarbamoyl)ethyl]-*N*-(3-chlorophenyl)-2-chloroacetamide

- A solution of the product from Step B (77 g, *ca.* 282 mmol) and triethylamine (67 mL, 480 mmol) in 500 mL of CH₂Cl₂ was cooled to 0°C. Chloroacetyl chloride (25.5 mL, 320 mmol) was added dropwise, and the reaction was maintained at 0°C with stirring. After 3 h, another portion of chloroacetyl chloride (3.0 mL) was added dropwise. After 30 min, the reaction was poured into EtOAc (2 L) and washed with water, sat. aq. NH₄Cl soln, sat. aq. NaHCO₃ soln., and brine. The solution was dried (Na₂SO₄), filtered, and concentrated *in vacuo* to provide the chloroacetamide as a brown oil which was used in the next step without further purification.

Step D: 4-(*tert*-butoxycarbonyl)-1-(3-chlorophenyl)-2-piperazinone

- To a solution of the chloroacetamide from Step C (*ca.* 282 mmol) in 700 mL of dry DMF was added K₂CO₃ (88 g, 0.64 mol). The solution was heated in an oil bath at 70-75°C for 20 hours, cooled to room temperature, and concentrated *in vacuo* to remove *ca.* 500 mL of DMF. The remaining material was poured into 33% EtOAc/hexane, washed with water and brine, dried (Na₂SO₄), filtered, and concentrated *in vacuo* to provide the product as a brown oil. This material was purified by silica gel chromatography (25-50% EtOAc/hexane) to yield

pure product, along with a sample of product (ca. 65% pure by HPLC) containing a less polar impurity.

Step E: 1-(3-chlorophenyl)-2-piperazinone

- 5 Through a solution of Boc-protected piperazinone from Step D (17.19 g, 55.4 mmol) in 500 mL of EtOAc at -78°C was bubbled anhydrous HCl gas. The saturated solution was warmed to 0°C, and stirred for 12 hours. Nitrogen gas was bubbled through the reaction to remove excess HCl, and the mixture was warmed to room temperature.
- 10 The solution was concentrated *in vacuo* to provide the hydrochloride as a white powder. This material was taken up in 300 mL of CH₂Cl₂ and treated with dilute aqueous NaHCO₃ solution. The aqueous phase was extracted with CH₂Cl₂ (8 x 300 mL) until tlc analysis indicated complete extraction. The combined organic mixture was dried
- 15 (Na₂SO₄), filtered, and concentrated *in vacuo* to provide the titled free amine as a pale brown oil.

Step E: 1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)imidazolylmethyl]-2-piperazinone dihydrochloride

- 20 To a solution of the amine from Step E (55.4 mmol, prepared above) in 200 mL of 1,2-dichloroethane at 0°C was added 4Å powdered molecular sieves (10 g), followed by sodium triacetoxyborohydride (17.7 g, 83.3 mmol). The imidazole carboxaldehyde from Step E of Example 4 (11.9 g, 56.4 mmol) was added, and the reaction was
- 25 stirred at 0°C. After 26 hours, the reaction was poured into EtOAc, washed with dilute aq. NaHCO₃, and the aqueous layer was back-extracted with EtOAc. The combined organics were washed with brine, dried (Na₂SO₄), filtered, and concentrated *in vacuo*. The resulting product was taken up in 500 mL of 5:1 benzene:CH₂Cl₂, and propyl-
- 30 amine (20 mL) was added. The mixture was stirred for 12 hours, then concentrated *in vacuo* to afford a pale yellow foam. This material was purified by silica gel chromatography (2-7% MeOH/CH₂Cl₂), and the resultant white foam was taken up in CH₂Cl₂ and treated with 2.1 equivalents of 1 M HCl/ether solution. After concentrated *in vacuo*,

the product dihydrochloride was isolated as a white powder.

EXAMPLE 3

5 Preparation of N-(2(R)-amino-3-mercaptopropyl)-valyl-isoleucyl-leucine methyl ester (Compound 3-1)

10 Step A. Preparation of N-(2(R)-t-butoxycarbonyl-amino-3-triphenyl-methylmercaptopropyl)-valyl-isoleucyl-leucine methyl ester

15 The tripeptide ester valyl-isoleucyl-leucine methyl ester was synthesized using conventional solution phase peptide synthesis methods. The trifluoroacetate salt of this tripeptide (360 mg, 0.77 mmol) was dissolved in 5 mL of methanol with 147 mg (1.5 mmol) of potassium acetate and 670 mg (1.5 mmol) of N-Boc-S-tritylcysteinal (prepared using the procedure of Goel, Krolls, Stier, and Kesten Org. Syn. 67: 69-74 (1988) for the preparation of N-Boc-leucinal) was added. Sodium cyanoborohydride (47 mg, 0.75 mmol) was added and the mixture was stirred overnight. The mixture was diluted with ether and washed with water, 5% ammonium hydroxide and brine. The solution was dried (sodium sulfate) and evaporated to give a white foam which was purified by chromatography (1-15% acetone in methylene chloride). The title compound was obtained as an oily material.

25 Step B. Preparation of N-(2(R)-amino-3-mercaptopropyl)-valyl-isoleucyl-leucine methyl ester

30 A sample of the protected pseudopeptide prepared as described in Step A (728 mg, 0.92 mmol) was dissolved in 100 mL of methylene chloride, 50 mL of TFA was added and the resulting yellow solution was treated immediately with 0.80 mL (5 mmol) of triethylsilane. After 45 min, the solvents were evaporated and the residue was partitioned between hexane and 0.1% aqueous TFA. The aqueous solution was lyophilized. This material was further purified by reverse phase HPLC (5-95% acetonitrile/0.1% TFA/water) to afford the title compound. ¹H NMR (CD₃OD) δ 8.65 (1H, d), 4.45 (1H, m), 4.3 (1H,

35

d), 3.7 (3H, s), 3.4 (1H, m), 3.15 (1H, d), 2.75-2.95 (m), 0.8-1.05 (18 H, m). FAB mass spectrum, $m/z = 447$ ($M + 1$).

Anal. Calcd for $C_{21}H_{42}N_4O_4S \cdot 1.8$ TFA:

C, 45.24; H, 6.75; N, 8.56.

5 Found: C, 45.26; H, 6.77; N, 8.50.

EXAMPLE 4

N-(2(R)-amino-3-mercaptopropyl)-valyl-isoleucyl-leucine

10 (Compound 7-2)

Step A. Preparation of N-(2(R)-t-butoxycarbonylamino-3-triphenylmethylmercaptopropyl)-valyl-isoleucyl-leucine

The product of Example 3, Step A (60 mg, 0.076 mmol)

15 was dissolved in 1 mL of methanol and 150 μ L of 1N NaOH was added. After stirring overnight, the solution was acidified with 150 μ L of 10% citric acid and the product was extracted with ether. The ether solution was washed with water and brine and dried (sodium sulfate). Evaporation provided the title compound as a solid.

20

Step B. Preparation of N-(2(R)-amino-3-mercaptopropyl)-valyl-isoleucyl-leucine

Using the method of Example 3, Step B, the protecting groups were removed with TFA and triethylsilane to provide the title

25 compound. FAB mass spectrum, $m/z = 433$ ($M+1$).

Anal. Calcd for $C_{20}H_{40}N_4O_4S \cdot 2$ TFA:

C, 43.63; H, 6.41; N, 8.48.

Found: C, 43.26; H, 6.60; N, 8.49.

EXAMPLE 5

- Preparation of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]pentyl-oxy-3-phenylpropionyl-homoserine lactone (Compound 5-1) and 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]pentyl-oxy-3-phenyl-propionyl-homoserine (Compound 5-2)

Step A: Preparation of N-(α -chloroacetyl)-L-isoleucinol

- To a stirred solution of L-isoleucinol (20 g, 0.17 mol) and triethylamine (28.56 ml, 0.204 mol) in CH_2Cl_2 (500 ml) at -78°C was added chloroacetyl chloride (16.3 ml, 0.204 mol) over 5 minutes. The cooling bath was removed and the solution allowed to warm to -20°C . The mixture was diluted with EtOAc and washed sequentially with 1 M HCl, and brine and dried (Na_2SO_4). Evaporation in vacuo afforded the amide title compound (35 g, 100%).
 $\text{Rf} = 0.3$ CH_2Cl_2 : MeOH (95:5);
 ^1H NMR (CDCl_3) δ 6.80 (1H, brd, $J = 5$ Hz), 4.10 (2H, s), 3.84 (1H, m), 3.79 (2H, m), 2.65 (1H, brs), 1.72 (1H, m), 1.55 (1H, m), 1.17 (1H, m), 0.96 (3H, d, $J = 6\text{Hz}$) 0.90 (3H, t, $J = 6$ Hz).

Step B: Preparation of 5(S)-[1(S)-methyl]propyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-3-one

- To a stirred solution of N-(α -chloroacetyl)-L-isoleucinol (7.4 g, 0.038 mol) in THF (125 ml) under argon at 0°C was slowly added sodium hydride (2.2 g of a 60% dispersion in mineral oil, 0.055 mol) with concomitant gas evolution. After completing the addition, the mixture was warmed to room temperature (R.T.) and stirred for 16 hr. Water (2.8 ml) was added and the solvents evaporated in vacuo. The residue was dissolved in CHCl_3 (70 ml) and washed with water saturated NaCl solution. The organic layer was dried (Na_2SO_4) and evaporated in vacuo. The residue was chromatographed using silica gel eluting with CH_2Cl_2 :MeOH (96:4) to afford the lactam title compound (4.35 g, 72%) as a white solid.
 $\text{Rf} = 0.35$ CH_2Cl_2 :MeOH (95:5);

¹H NMR δ (CDCl₃) 6.72 (1H, brs), 4.20 (1H, d, J = 14.5 Hz), 4.10 (1H, d, J = 14.5 Hz), 3.88 (1H, dd, J = 9 and 3.5 Hz), 3.58 (1H, dd, J = 9 and 6.5 Hz), 3.45 (1H, brqt, J = 3.5 Hz), 1.70-1.45 (2H, m), 1.34 - 1.15 (1H, m), 0.96 (3H, t, J = 6.5 Hz), 0.94 (3H, d, J = 6.5 Hz).

5

Step C: Preparation of N-(tert-butoxycarbonyl)-5(S)-[1(S)-methyl]propyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-3-one

5(S)-[1(S)-Methyl]propyl-2,3,5,6-tetrahydro 4H-1,4-oxazin-3-one (12.2 g, 0.0776 mol) and DMAP (18.9 g, 0.155 mol) were dissolved in methylene chloride (120 ml) under argon at R.T. Boc anhydride (33.9 g, 0.155 mol) was added to the stirred solution in one portion, with concomitant gas evolution and the mixture was stirred at R.T. for 16 hr. The solvent was evaporated in vacuo and the residue was taken up in ethyl acetate and washed sequentially with 10% citric acid, 50% NaHCO₃ and finally brine. The organic extract was dried

15

(Na₂SO₄) and evaporated in vacuo. Chromatography of the residue over silica gel eluting with 20% EtOAc in hexanes afforded the title compound (14.1 g, 71%) as a white solid.

R_f = 0.75 EtOAc:hexanes (20:80); mp 59-60°C

20

Anal. Calc'd. for C₁₃H₂₃O₄N :

C, 60.68; H, 9.01; N, 5.44.

Found: C, 60.75; H, 9.01; N, 5.58.

¹H NMR (CDCl₃) δ 4.25 (1H, d, J = 15 Hz), 4.15 (1H, d, J = 15 Hz), 4.15 - 4.00 (2H, m), 3.73 (1H, dd, J = 10 and 2 Hz), 1.88 (1H, qt, J = 6 Hz), 1.55 (9H, s), 1.50 - 1.36 (1H, m), 1.35 - 1.19 (1H, m) 1.00 (3H, d, J = 6 Hz) 0.95 (3H, d, J = 6.5 Hz).

25

Step D: Preparation of N-(tert-Butoxycarbonyl)-2(S)-benzyl-5(S)-[1(S)-methyl]propyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-3-one

30

A solution of N-(tert-butoxycarbonyl)-5(S)-[1(S)-methyl]propyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-3-one (5.75 g, 22.34 mmol) in DME (100 ml) under argon was cooled to -60°C. The cold solution was transferred via canula to a second flask containing sodium

bis(trimethylsilyl)amide (24.58 ml of a 1M solution in THF, 24.58 mmol) at -78°C under argon. After stirring for 10 minutes, benzyl bromide (2.25 ml, 18.99 mmol) was added over 5 minutes and the resulting mixture was stirred at -78°C for 3 hours. After this time, the reaction mixture was transferred via cannula to another flask containing sodium bis(trimethylsilyl)amide (24.58 ml of a 1M solution in THF, 24.58 mmol) at -78°C, under argon. After stirring for a further 5 minutes, the reaction was quenched by the addition of saturated aqueous ammonium chloride solution (24.6 ml) and allowed to warm to room temperature. This mixture was diluted with brine (50 ml) and water (20 ml) and then extracted with ethyl acetate (2 x 100 ml). The organic extracts were washed with brine (50 ml) and evaporated in vacuo to afford an oil. Chromatography of the residue over silica gel (230-400 mesh, 300 g) eluting with 10-20% ethyl acetate in hexanes afforded the title compound (5.12 g, 67%) as a clear oil.

R_f = 0.25 EtOAc:Hexanes (20:80);
1H NMR (CDCl₃) δ 7.35 - 7.15 (5H, m), 4.31 (1H, dd, J = 6 and 2 Hz), 4.03 (1H, d, J = 12 Hz), 3.88 (1H, dd, J = 6 and 1 Hz), 3.66 (1H, dd, J = 12 and 2 Hz), 3.29 (1H, dd, J = 12 and 3 Hz), 1.54 (9H, s), 3.12 (1H, dd, J = 12 and 7 Hz), 1.47 (1H, m), 1.25 (1H, m), 1.10 (1H, m), 0.83 (3H, d, J = 6 Hz), 0.80 (3H, t, J = 6 Hz).

Step E: Preparation of N-(tert-butoxycarbonyl)-2(S)-[2(S)-amino-3(S)-methyl]pentyloxy-3-phenyl-propionic acid

To a stirred solution of N-(tert-butoxycarbonyl)-2(S)-benzyl-5(S)-[1(S)-methyl]-propyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-3-one (5.1 g, 14.7 mmol) in THF (150 ml) and water (50 ml) at 0°C was added hydrogen peroxide (15 ml of a 30% aqueous solution, 132 mmol) and lithium hydroxide (3.0 g, 63.9 mmol). After stirring for 30 minutes, the reaction was quenched with a solution of sodium sulfite (28.25 g, 0.224 mol) in water (70 ml). The THF was evaporated in vacuo and the aqueous phase was acidified to pH 3-4 by addition of 10% citric acid solution and extracted with EtOAc. The organic extracts were dried (Na₂SO₄), evaporated in vacuo and the residue purified

by chromatography over silica gel eluting with 4% MeOH in CH₂Cl₂ to give the lactam 2(S)-benzyl-5(S)-[1(S)-methyl]propyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-3-one (0.82 g 22%) and then with 20% MeOH in CH₂Cl₂ to afford the title compound (4.03 g, 75%) as a viscous oil.

5 R_f = 0.4 MeOH:CH₂Cl₂ (5:95) + 0.3% AcOH;

¹H NMR (d₆ DMSO) δ 7.35 - 7.10 (5H, m), 6.68 (1H, br, s), 3.75 (1H, dd, J = 7.5 and 2.5 Hz) 3.54 (1H, m), 3.5 - 3.2 (2H, m) 2.99 (1H, dd, J = 12.5 and 2.5 Hz), 2.75 (1H, dd, J = 12.5 and 7.5 Hz), 1.50 - 1.35 (11H, m), 0.98 (1H, sept, J = 6 Hz), 0.78 (3H, t, J = 6 Hz), 0.65 (3H, d, J = 6 Hz);

10 FAB MS 366 (MH⁺) 266 (MH₂⁺ - CO₂tBu).

Step F: Preparation of N-(tert-butoxycarbonyl)-2(S)-[2(S)-amino-3(S)-methyl]-pentyloxy-3-phenyl-propionyl-homoserine
lactone

15 To a stirred solution of N-(tert-butoxycarbonyl)-2(S)-[2(S)-amino-3(S)-methyl]-pentyloxy-3-phenylpropionic acid (0.53 g, 1.45 mmol) and 3-hydroxy-1,2,3,-benzotriazin-4(3H)-one (HOOBT) (0.26 g, 1.6 mmol) in DMF (15 ml) at room temperature was added
20 EDC (0.307 g, 1.6 mmol) and L-homoserine lactone hydrochloride (0.219 g, 6.0 mmol). The pH was adjusted to pH= 6.5 by addition of NEt₃ (the pH was monitored by application of an aliquot of the reaction mixture to a moist strip of pH paper). After stirring at room temperature for 16 hr, the reaction was diluted with EtOAc and washed with
25 saturated NaHCO₃ and then brine and dried (NaSO₄). Evaporation in vacuo (sufficient to remove DMF) and chromatography over silica gel eluting with 5% acetone in CH₂Cl₂ afforded the title compound (520 mg, 80%) as a white solid, mp 115-117°C.

R_f = 0.3 Acetone: CH₂Cl₂ (5:95).

30 ¹H NMR (CDCl₃) δ 7.73 (1H, brd, J=5 Hz), 7.40-7.15 (5H, m), 4.68 (1H, dt, J=9 and 7.5 Hz), 4.65-4.35 (2H, m), 4.33-4.18 (1H, m), 4.20 (1H, dd, J=7 and 3 Hz), 3.78 (1H, m), 3.49 (1H, dd, J=7.5 and 4.0 Hz), 3.37 (1H, dd, J=7.5 and 6.5 Hz), 3.15 (1H, dd, J=11.5 and 2 Hz), 2.86 (1H, dd, J=11.5 and 7.5 Hz), 2.68 (1H, m) 2.11 (1H, q, J=9 Hz), 1.55-

1.30 (11H, m), 1.07 (1H, m), 0.87 (3H, t, J=6.3 Hz), 0.79 (3H, d, J=6 Hz).

Step G: Preparation of 2(S)-[2(S)-amino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-homoserine lactone hydrochloride

Anhydrous HCl gas was bubbled through a cold (0°C) solution of N-(tert-butoxycarbonyl)-2(S)-[2(S)-amino-3(S)-methyl] pentyloxy-3-phenylpropionyl-homoserine lactone (3.0 g, 6.7 mmol) in ethyl acetate (120 ml) until a saturated solution was obtained. The resulting mixture was stirred at 0°C for 1 hr. The solution was purged with nitrogen and the mixture concentrated in vacuo to afford the title compound as a sticky foam which was used without further purification. ¹H NMR (d₆ DMSO) δ 8.60 (1H, d, J=7 Hz), 8.08 (3H, brs), 7.35-7.15 (5H, m), 4.60 (1H, qt, J=8 Hz), 4.36 (1H, t J=7.5 Hz), 4.22 (1H, q, J=7.5 Hz), 4.15-3.95 (2H, m), 3.64 (1H, dd, J=9 and 2.5 Hz), 3.15-3.00 (2H, m), 2.92 (1H, dd, J=12.5 and 5.0 Hz), 2.40-2.15 (2H, m), 1.65 (1H, m), 1.43 (1H, m), 1.07 (1H, m), 0.82 (3H, t, J=6 Hz), 0.72 (3H, d, J=6.0 Hz).

Step H: Preparation of 2(S)-[2(S)-[2(R)-(tert-butoxycarbonyl)-amino-3-triphenylmethylmercap-to]propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-homoserine lactone

2(S)-[2(S)-Amino-3(S)-methyl]pentyloxy-3-phenylpropionyl-homoserine hydrochloride (6.7 mmol) and N-(tert-butoxycarbonyl)-S-triphenylmethylcysteine aldehyde (0.74 g, 7.5 mmol) (prepared from N-(tert-butoxycarbonyl)-S-triphenylmethylcysteine by the procedure of Goel, O.P.; Krolls, U.; Stier, M.; Keston, S. Org. Syn. 1988, 67, 69.) and potassium acetate (3.66 g, 8.2 mmol) were dissolved in methanol (48 ml). Activated 4A molecular sieves (6g) and then Na(CN)BH₃ (0.70 g, 10.7 mmol) were added and the resulting slurry was stirred under argon at room temperature for 16 hr. The solids were removed by filtration and the filtrate evaporated in vacuo. The residue was dissolved in EtOAc and washed sequentially with saturated aqueous NaHCO₃ and brine and then dried (Na₂SO₄). Evaporation in

vacuo afforded an oil which was purified by chromatography over silica gel eluting with a gradient of 30-50% EtOAc in hexane to afford the title compound (2.34 g, 45%) contaminated with a small amount of the corresponding methyl ester.

- 5 ¹H NMR (CD₃OD) δ 7.60-7.05(20H, m), 4.64 (1H, d, J=9.0Hz), 4.39 (1H, br t, J=9Hz), 4.25(1H, m), 3.93 (1H, m), 3.75-3.60(1H, m), 3.55 (1H, dd, J=9.0 and 2Hz), 3.20 (1H, dd, J=9.0 and 6.0 Hz), 3.04 (1H, dd, J=15.0 and 5.0 Hz), 2.85 (1H, dd, J=15.0 and 9.0 Hz), 2.60 (1H, dd, J=12.0 and 5.0 Hz), 2.50-2.15 (7H, m), 1.45 (9H, s), 1.40-1.20 (1H, m),
10 1.07 (1H, m), 0.87 (3H, t, J=6 Hz), 0.67 (3H, d, J=6.0 Hz).

Step I: Preparation of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-homoserine lactone

- 15 To a stirred solution of 2(S)-[2(S)-[2(R)-(tert-butoxy-carbonyl)amino-3-triphenylmethylmercapto]-propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-homoserine lactone (2.72 g, 3.49 mmol) in CH₂Cl₂ (90 ml) was added HSiEt₃ (2.16 ml, 13.5 mmol) and TFA (43.2 ml, 0.56 mol) and the solution was stirred at R.T. under
20 argon for 2 hrs. The solvent was evaporated in vacuo and the residue partitioned between 0.1% aqueous TFA (200 ml) and hexanes (100 ml). The aqueous layer was separated and washed with hexanes (20 ml) and then lyophilised. The resulting white lyophilate was chromatographed
25 in 5 equal portions over a Waters Prepak cartridge (C-18, 15-20 mM 100 Å) eluting with a gradient of 95:5 to 5:95 0.1% TFA in H₂O : 0.1% TFA in CH₃CN at 100 ml/min over 60 min. The desired compound eluted after 19 min. The CH₃CN was evaporated in vacuo and the aqueous solution lyophilised to afford the title compound (1.95 g, 77%)
as the TFA salt.
30 The salt is hygroscopic and is prone to disulphide formation if left in solution and exposed to air.
¹H NMR δ (CD₃OD) 7.40-7.15 (5H,m), 4.55-5.40 (2H, m), 4.33 (1H, m), 4.18 (1H, m), 3.90-3.62 (3H, m), 3.53 (1H, dd, J=10.5 and 4.0 Hz),

3.37 (1H, dd, J=10.5 and 6.0 Hz), 3.23 (1H, m), 3.15-2.95 (2H, m), 2.88 (1H, dd, J=12.5 and 5.0 Hz), 2.55-2.25 (2H, m), 1.92 (1H, m), 1.49 (1H, m), 1.23 (1H, m), 0.94 (3H, t, J=6 Hz), 0.90 (3H, d, J=6Hz).
FAB MS 873 (2M-H⁺) 438 (MH⁺) 361 (MH⁺Ph)

5 Anal. calc'd for C₂₂H₃₆O₄N₃S 2.6 TFA:

C, 43.58; H, 5.25; N, 5.82.

Found: C, 43.62; H, 5.07; N, 5.80.

Step J: Preparation of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]pentylloxy-3-phenylpropionyl-homoserine
10
2(S)-[2(S)-[2(R)-Amino-3-mercapto]propyl-amino-3(S)-methyl]pentylloxy-3-phenylpropionyl-homoserine lactone (0.00326 mmol) was dissolved in methanol (0.0506 ml) and 1N sodium hydroxide
15 (0.0134 ml) was added followed by methanol (0.262 ml). The conversion of the lactone to the hydroxy-acid was confirmed by HPLC analysis and NMR.

EXAMPLE 6

20 Preparation of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]pentylloxy-3-phenylpropionyl-methionine

Step A: Preparation of 2(S)-[2(S)-[2(R)-(tert-butoxy-carbonyl)-amino-3-triphenyl-methylmercapto]-propylamino-3(S)-methyl]pentylloxy-3-phenylpropionyl-methionine
25
To a solution of 2(S)-[2(S)-[2(R)-(tert-butoxycarbonyl)-amino-3-triphenylmethylmercapto]-propylamino-3(S)-methyl]-pentylloxy-3-phenylpropionyl-methionine methyl ester (120 mg, 0.143 mmol) in methanol (4 ml) was added sodium hydroxide (1N, 0.57 ml, 0.57 mmol) and the resulting mixture was stirred at room temperature
30 for 3 hours. Another portion of sodium hydroxide (1N, 0.25 ml) was added and stirring continued for 0.5 hours. The reaction mixture was concentrated and the residue was dissolved in a minimum amount of

water and neutralized with hydrochloric acid (1N, 0.87 ml). The aqueous solution was extracted with ethyl acetate three times. The combined extracts were dried (Na₂SO₄) and concentrated to yield the title compound (110 mg, 0.133 mmol, 93%). NMR (CD₃OD) δ 0.70

- 5 (3H, d, J=6Hz), 0.80 (3H, t, J=6Hz), 1.05 (H, m), 1.34 (9H, s), 1.60 (H, m), 1.95 (3H, s), 2.7~2.9 (3H, m), 2.95~3.1 (2H, m), 3.95 (H, d of d, J=8, 4Hz), 4.27 (H, d of d, J=8.6Hz), 7.1~7.4 (20H, m).

- 10 Step B: Preparation of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]pentylloxy-3-phenylpropionyl-methionine

- The title compound was prepared in the same manner as that described in Example 5, Step I, but using 2(S)-[2(S)-[2(R)-(tert-butoxycarbonyl)-amino-3-triphenylmethylmercapto]-propylamino-3(S)-methyl]-pentylloxy-3-phenylpropionyl-methionine in place of 2(S)-[2(S)-[2(R)-(tert-butoxycarbonyl)-amino-3-triphenylmethylmercapto]-propylamino-3(S)-methyl]-pentylloxy-3-phenylpropionyl-homoserine lactone. NMR (CD₃OD) δ 0.82 (3H, d, J=6Hz), 0.95 (3H, t, J=6Hz), 1.20 (H, m), 1.40 (H, m), 1.85 (H, m), 2.10 (3H, s), 2.4~2.6 (2H, m), 3.1~3.2 (2H, m), 3.35 (H, d of d, J=14, 6Hz), 3.55 (H, d of d, J=14, 5Hz), 4.20 (H, d of d, J=10, 5Hz), 4.63 (H, d of d, J=10.6Hz), 7.27 (5H, m).

- 20 Anal. Calcd for C₂₃H₃₉N₃O₄S₂•2CF₃CO₂H•2H₂O:

- C, 43.25; H, 6.05; N, 5.60.
25 Found: C, 43.09; H, 6.01; N, 5.46.

EXAMPLE 7

Preparation of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]pentyl-3-phenylpropionyl-methionine sulfone methyl ester
(Compound 7-1)

Step A: Preparation of Methionine sulfone methyl ester

Thionyl chloride (2.63 ml, 36 mmol) was added dropwise to a stirred solution of N-Boc-Met sulfone (5 g, 18 mmol) in methanol (40 ml) cooled at 0°C. After the completion of the addition, the resulting mixture was warmed to room temperature and stirred overnight. The reaction mixture was recooled to 0°C and slowly treated with solid sodium bicarbonate to adjust the pH to 7. The mixture was concentrated in vacuo to remove methanol and the residue was dissolved in a minimum amount of water (solution pH ca. 10) and extracted with ethyl acetate four times. The combined extracts were dried (Na₂SO₄) and concentrated to give the title compound (1.5 g). NMR (CD₃OD) δ 2.04 (H, m), 2.21 (H, m), 2.98 (3H, s), 3.23 (2H, t, J=7Hz), 3.63 (H, d of d, J=8.6Hz), 3.77 (3H, s).

Step B: Preparation of N-(tert-Butoxycarbonyl)-2(S)-[2(S)-amino-3(S)-methyl]-pentyl-3-phenyl-propionyl-methionine sulfone methyl ester

The title compound was prepared in the same fashion as that described in Example 8, Step F, but using methionine sulfone methyl ester in place of homoserine lactone hydrochloride. NMR (CD₃OD) δ 0.80 (3H, d, J=6Hz), 0.88 (3H, t, J=6Hz), 1.12 (H, m), 1.47 (9H, s), 2.10 (H, m), 2.32 (H, m), 2.93 (3H, s), 3.5~3.7 (2H, m), 3.74 (3H, s), 4.01 (H, d of d, J=7.4Hz), 4.60 (H, d of d, J=9.5Hz), 6.60 (H, d, J=8Hz), 7.25 (5H, m).

Step C: Preparation of 2(S)-[2(S)-Amino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone methyl ester hydrochloride

The title compound was prepared in the same fashion as that described in Example 5, Step G, but using N-(tert-butoxycarbonyl)-2(S)-[2(S)-amino-3(S)-methyl]pentyloxy-3-phenylpropionyl-methionine sulfone methyl ester in place of N-(tert-butoxycarbonyl)-2(S)-[2(S)-amino-3(S)-methyl]pentyloxy-3-phenylpropionyl-homoserine lactone. NMR (CD₃OD) δ 0.85 (3H, d, J=6Hz), 0.94 (3H, t, J=6Hz), 1.20 (H, m), 1.52 (H, m), 1.72 (H, m), 2.14 (H, m), 2.38 (H, m), 2.98 (3H, s), 3.57 (H, d of d, J=12, 6Hz), 3.73 (H, d of d, J=12, 9Hz), 3.78 (3H, s), 4.15 (H, d of d, J=8.6Hz), 4.63 (H, d of d, J=8.5Hz), 7.30 (5H, m).

Step D: Preparation of 2(S)-[2(S)-[2(R)-(tert-Butoxy-carbonyl)-amino-3-triphenylmethyl]mercapto]-propylamino-3(S)-methyl]pentyloxy-3-phenyl-propionyl-methionine sulfone methyl ester

The title compound was prepared in a similar fashion as that described in Example 5, Step H, but using 2(S)-[2(S)-amino-3(S)-methyl]pentyloxy-3-phenyl-propionyl-methionine sulfone methyl ester hydrochloride in place of 2(S)-[2(S)-amino-3(S)-methyl]pentyloxy-3-phenylpropionyl-homoserine lactone hydrochloride. NMR (CD₃OD) δ 0.70 (3H, d, J=6Hz), 0.88 (3H, t, J=6Hz), 1.10 (H, m), 1.47 (9H, s), 2.15 (H, m), 2.67 (H, m), 2.92 (3H, s), 3.67 (H, m), 4.68 (H, d of d, J=10, 6Hz), 7.15-7.45 (20H, m).

Step E: Preparation of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-methionine sulfone methyl ester

The title compound was prepared in a similar fashion as that described in Example 5, Step I, but using 2(S)-[2(S)-[2(R)-(tert-butoxycarbonyl)amino-3-triphenylmethyl]mercapto]propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone methyl ester in place of 2(S)-[2(S)-[2(R)-(tert-butoxy-carbonyl)-amino-3-triphenyl-

- methylmercapto]propylamino-3(S)-methyl]pentyloxy-3-phenyl-
 propionyl-homoserine lactone. NMR (CD₃OD) δ 0.83 (3H, d, J=6Hz),
 0.93 (3H, t, J=6Hz), 1.20 (H, m), 1.51 (H, m), 1.80 (H, m), 2.22 (H, m),
 2.43 (H, m), 3.00 (3H, s), 3.78 (3H, s), 4.20 (H, d of d, J=8.4Hz), 4.72
 5 (H, d of d, J=10, 6Hz), 7.30 (5H, m).
 FABMS m/z 532 (MH⁺).

EXAMPLE 8

- 10 Preparation of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-
methyl]pentyloxy-3-phenylpropionyl-methionine sulfone (Compound 8-
1)

- 15 Step A: Preparation of 2(S)-[2(S)-[2(R)-(tert-Butoxy-carbonyl)-
 amino-3-triphenylmethylmercapto]-propylamino-3(S)-
methyl]pentyloxy-3-phenylpropionyl-methionine sulfone
 The title compound was prepared in a similar fashion as
 that described in Example 6, Step A, but using 2(S)-[2(S)-[2(R)-(tert-
 20 butoxycarbonyl)amino-3-triphenylmethylmercapto]-propylamino-3(S)-
 methyl]pentyloxy-3-phenylpropionyl-methionine sulfone methyl ester
 in place of 2(S)-[2(S)-[2(R)-(tert-butoxycarbonyl)amino-3-triphenyl-
 methylmercapto]propylamino-3(S)-methyl]pentyloxy-methionine methyl
 ester. NMR (CD₃OD) δ 0.79 (3H, d, J=6Hz), 0.90 (3H, t, J=6Hz), 1.47
 (9H, s), 2.92 (3H, s), 4.08 (H, m), 4.32 (H, m), 7.15~7.35 (20H, m).

- 25 Step B: Preparation of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-
 propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-
methionine sulfone

- 30 The title compound was prepared in a similar fashion as
 that described in Example 5, Step I, but using 2(S)-[2(S)-[2(R)-(tert-
 butoxycarbonyl)amino-triphenylmethylmercapto]propylamino-3(S)-
 methyl]pentyloxy-3-phenylpropionyl-methionine sulfone in place
 of 2(S)-[2(S)-[2(R)-(tert-butoxycarbonyl)amino-3-triphenylmethyl-
 mercapto]propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-

3(S)-methyl]pentyloxy-3-phenylpropionyl-homoserine lactone. NMR (CD₃OD) δ 0.84 (3H, d, J=6Hz), 0.94 (3H, t, J=6Hz), 1.21 (H, m), 1.50 (H, m), 1.82 (H, m), 2.24 (H, m), 2.47 (H, m), 2.98 (3H, s), 3.6-3.75 (3H, m), 4.20 (H, d of d, J=9.5Hz), 4.64 (H, d of d, J=9.6Hz), 7.30

5 (5H, m).

Anal. Calcd for C₂₃H₃₉N₃O₆S₂•3CF₃CO₂H:

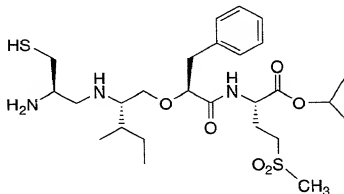
C, 40.51; H, 4.92; N, 4.89.

Found: C, 40.47; H, 5.11; N, 4.56.

10

EXAMPLE 9

Preparation of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-methionine sulfone isopropyl ester (Compound A)



15

The title compound was prepared using methods A-E from Example 7, except for Method A. Methionine sulfone isopropyl ester was prepared by coupling t-butyloxycarbonyl-methionine sulfone with isopropyl alcohol using dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) followed by deprotection with HCl in EtOAc. NMR (CD₃OD) δ 0.83 (3H, d, J = 6 Hz), 0.94 (3H, t, J = 6 Hz), 1.11-1.56 (2H, m), 1.28 (6H, d, J = 6 Hz), 1.8-1.96 (1H, m), 2.12-2.27 (1H, m), 2.89-3.0 (2H, m), 3.01 (3H, s), 3.06-3.3 (4H, m), 3.42 (1H, dd, J = 6, 13 Hz), 3.65 (1H, dd, J = 6, 13 Hz), 3.68-3.91 (3H, m), 4.2-4.27 (1H, m), 4.61-4.7 (1H, m), 4.96-5.12 (2H, m), 7.19-7.44 (5H, m).

20

25

Anal. Calc'd. for $C_{26}H_{45}N_3O_6S_2 \cdot 2 CF_3CO_2H$:

C, 44.07; H, 5.67; N, 4.97;

Found: C, 44.35; H, 5.68; N, 5.23

5

EXAMPLE 10

4-[1-(5-Chloro-2-oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-pyrrol-2-ylmethyl]-benzonitrile

10

Step 1: 5-Chloro-5'-methyl-[1,2']bipyridinyl-2-one

5-Chloro-2-pyridinol (2.26g, 17.4 mmol), 2-bromo-5-methylpyridine (3.00g, 17.4 mmol), copper (0.022g, 0.35 mmol) and K_2CO_3 (2.66g, 19.2 mmol) were heated at 180°C for 16 hrs. The brown reaction mixture was cooled, diluted with EtOAc and washed with saturated $NaHCO_3$. The aqueous layer was extracted with EtOAc (2x) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated in vacuo. The residue was chromatographed (silica gel, EtOAc: CH_2Cl_2 20:80 to 50:50 gradient elution) to afford the title compound as a white solid.

1H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.96(d, J=3.0Hz, 1H), 7.83 (d, J=8.4Hz, 1H), 7.65(dd, J=2.4 and 8.2Hz, 1H), 7.32(dd, J=2.9 and 9.7 Hz, 1H), 6.61(d, J=9.7Hz, 1H) and 2.39(s,3H)ppm.

25 Step 2: 5'-Bromomethyl-5-chloro-[1,2']bipyridinyl-2-one

A solution of the pyridine from Step 1(1.00g, 4.53 mmol), N-bromosuccinimide (0.81g, 4.53 mmol) and AIBN (0.030g, 0.18 mmol) in CCl_4 (40mL) was heated at reflux for 2 hrs. The solids were filtered and the filtrate collected. The solvent was evaporated in vacuo and the residue chromatographed (silica gel, EtOAc: CH_2Cl_2 25:75 to 50:50 gradient elution) to afford the title bromide.

1H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.04(d, J= 2.9 Hz, 1H), 8.01 (d, J=8.4Hz, 1H), 7.88 (dd, J=2.4 and 8.6Hz, 1H), 7.34(dd, J= 2.9 and 9.8Hz, 1H), 6.61(d, J=9.9Hz, 1H) and 4.51 (s,2H) ppm.

Step 3: 4-[1-(5-Chloro-2-oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-
1H-pyrrol-2-ylmethyl]-benzonitrile hydrochloride

- 5 The bromide from Step 2 (0.750g, 2.50 mmol) and the
4-(1-trityl-1H-imidazol-4-ylmethyl)-benzonitrile (1.06g, 2.50 mmol)
in CH₃CN (10 mL) were heated at 60°C. The reaction was cooled to
room temperature and the solids collected by filtration and washed
with EtOAc (10mL). The solid was suspended in methanol (50 mL)
and heated at reflux for 1 hr, cooled and the solvent evaporated in
10 vacuo. The sticky residue was stirred in EtOAc (40mL) for 4 hrs and
the resulting solid hydrobromide salt collected by filtration and washed
with EtOAc (40mL) and dried in vacuo. The hydrobromide salt was
partitioned between sat. NaHCO₃ and CH₂Cl₂ and extracted with CH₂Cl₂.
The organic extracts were dried (Na₂SO₄) and evaporated in vacuo. The
15 residue was chromatographed (silica gel, MeOH: CH₂Cl₂ 4:96 to 5:95
gradient elution) to afford the free base which was converted to the
hydrochloride salt to afford the title compound as a white solid.
¹H NMR (400 MHz, CD₃OD) δ 9.11 (s, 1H), 8.35 (s, 1H), 8.03(d,
J=2.9Hz, 1H), 7.83 (d, J=8.4 Hz, 1H), 7.76 (dd, J=2.4 and 9.6Hz, 1H),
20 7.68-7.58 (m, 3H), 7.48 (s, 1H), 7.31(d, J=8.6Hz, 2H), 6.68 (d, J=9.3Hz,
1H), 5.53 (s, 2H) and 4.24 (s, 2H) ppm.

Analysis: Calc for C₂₂H₁₆N₅OCl: 1.75 HCl, 0.15 EtOAc

C 56.69, H 3.99, N 14.62

Found: C 56.72, H 4.05, N 14.54

25

EXAMPLE 11

- Preparation of (R)-1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)-5-
imidazolylmethyl]-5-[2-(ethanesulfonyl)methyl]-2-piperazinone
30 dihydrochloride

Step A: Preparation of (R)-2-(*tert*-butoxycarbonylamino)-N-(3-chlorophenyl)-3-[(triphenylmethyl)thio]-1-propanamine

To a solution of 3-chloroaniline (0.709 mL, 6.70 mmol) in 30 mL of dichloromethane at room temperature was added 1.2 g of crushed 4Å molecular sieves. Sodium triacetoxyborohydride (3.55 g, 16.7 mmol) was added, followed by dropwise addition of N-methylmorpholine to achieve a pH of 6.5. L-S-Trityl-N-Boc-cysteinal (3.15 g, 7.04 mmol) (prepared according to S.L. Graham et al. *J. Med. Chem.*, (1994) Vol. 37, 725-732) was added, and the solution was stirred for 48 hours. The reaction was quenched with sat. aq. NaHCO₃, diluted with EtOAc, and the layers were separated. The organic material was washed with brine, dried (Na₂SO₄), filtered, and concentrated *in vacuo* to provide an oil which was purified by silica gel chromatography (15% EtOAc/hexane) to give the title amine.

Step B: Preparation of (R)-N-[2-(*tert*-butoxycarbonylamino)-3-((triphenylmethyl)thio)propyl]-2-chloro-N-(3-chlorophenyl)acetamide

The aniline derivative from Step A (2.77 g, 4.95 mmol) was dissolved in 73 mL of EtOAc and 73 mL of sat. NaHCO₃ soln., then cooled to 0 °C. With vigorous stirring, chloroacetyl chloride (0.533 mL, 6.69 mmol) was added dropwise. After 3 hours, the reaction was diluted with water and EtOAc, and the organic layer was washed with brine, dried (Na₂SO₄), filtered, and concentrated *in vacuo* to provide crude titled chloroacetamide which was used without further purification.

Step C: Preparation of (R)-4-(*tert*-butoxycarbonyl)-1-(3-chlorophenyl)-5-[S-(triphenylmethyl)thiomethyl]piperazine-2-one

To a solution of chloroacetamide from Step B (3.29 g crude, theoretically 4.95 mmol) in 53 mL of DMF at 0°C was added cesium carbonate (4.84 g, 14.85 mmol). The solution was stirred for

- 48 hours, allowing it to warm to room temperature. The solution was poured into EtOAc, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the crude product as an oil. This material was purified by silica gel chromatography (20% EtOAc/hexane) to yield the product as a white solid.

Step D: Preparation of (R)-4-(*tert*-butoxycarbonyl)-1-(3-chlorophenyl)-5-(thiomethyl)piperazin-2-one

- A solution of piperazinone from Step C (625 mg, 1.04 mmol) in degassed EtOAc (38 mL) and EtOH (12 mL) was warmed to 30 °C. A solution of AgNO_3 (177 mg, 1.04 mmol) and pyridine (0.084 mL, 1.04 mmol) in 8 mL of EtOH was added, and the solution was heated to reflux. After 45 minutes, the reaction was concentrated *in vacuo*, then redissolved in 26 mL of degassed EtOAc. Through this solution was bubbled H_2S gas for 2.5 minutes, then activated charcoal was added after 4 minutes. The material was filtered through celite and rinsed with degassed EtOAc, concentrated *in vacuo*, then reconcentrated from degassed CH_2Cl_2 to provide the crude product which was used without further purification.

Step E: Preparation of (R)-4-(*tert*-butoxycarbonyl)-1-(3-chlorophenyl)-5-[(ethylthio)methyl]piperazin-2-one

- A solution of the thiol from Step D (*ca.* 1.04 mmol) in 3 mL of THF was added *via* cannula to a suspension of NaH (51.4 mg, 60% disp. in mineral oil, 1.28 mmol) in 2 mL THF at 0°C. After 10 minutes, iodoethane was added (0.079 mL, 0.988 mmol), and the solution was stirred for 1.5 hours. The reaction was poured into EtOAc, washed with sat. NaHCO_3 and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the crude product. This material was purified by silica gel chromatography (1% MeOH/ CH_2Cl_2) to yield the titled product.

Step F: Preparation of (R)-4-(*tert*-butoxycarbonyl)-1-(3-chlorophenyl)-5-[(ethanesulfonyl)methyl]piperazin-2-one

To a solution of the sulfide from Step E (217 mg, 0.563 mmol) in 3 mL of MeOH at 0 °C was added a solution of magnesium monoperoxyphthalate (835 mg, 1.69 mmol) in 2 mL MeOH. The reaction was stirred overnight, allowing it to warm to room temperature. The solution was cooled to 0 °C, quenched by the addition of 4 mL 2N Na₂S₂O₃ soln., then concentrated *in vacuo*. The residue was partitioned between EtOAc and sat NaHCO₃ solution, and the organic layer was washed with brine, dried (Na₂SO₄), filtered, and concentrated *in vacuo* to provide the crude sulfone as a white waxy solid.

Step G: Preparation of (R)-1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)methyl]-2-piperazinone dihydrochloride

To a solution of the Boc-protected piperazinone from Step F (224 mg, 0.538 mmol) in 5 mL of dichloromethane at 0°C was added 2.5 mL of trifluoroacetic acid (TFA). After 45 minutes, the reaction was concentrated *in vacuo*, then azeotroped with benzene to remove the excess TFA. The residue was taken up in 4 mL of 1,2-dichloroethane and cooled to 0°C. To this solution was added 4Å powdered molecular sieves (340 mg), followed by sodium triacetoxyborohydride (285 mg, 1.34 mmol) and several drops of triethylamine to achieve pH = 6. The imidazole carboxaldehyde from Step E of Example 42 (125 mg, 0.592 mmol) was added, and the reaction was stirred at 0°C. After 2 days, the reaction was poured into EtOAc, washed with dilute aq. NaHCO₃, and brine, dried (Na₂SO₄), filtered, and concentrated *in vacuo*. The crude product was taken up in methanol and injected onto a preparative HPLC column and purified with a mixed gradient of 15%-50% acetonitrile/0.1% TFA; 85%-50% 0.1% aqueous TFA over 60 minutes. After concentration *in vacuo*, the resultant product was partitioned between dichloromethane and aq. NaHCO₃ soln., and the aqueous phase was extracted with CH₂Cl₂. The organic solution was washed with brine, dried (Na₂SO₄), filtered, and concentrated to dryness to provide the

product free base, which was taken up in CH_2Cl_2 and treated with 2.1 equivalents of 1 M HCl/ether solution. After concentrated *in vacuo*, the product dihydrochloride was isolated as a white powder.

5 BIOLOGICAL ASSAYS.

The ability of compounds of the present invention to inhibit cancer can be demonstrated using the following assays.

In vitro inhibition of farnesyl-protein transferase

- 10 *Transferase Assays.* Isoprenyl-protein transferase activity assays were carried out at 30°C unless noted otherwise. A typical reaction contained (in a final volume of 50 μL): [^3H]farnesyl diphosphate or [^3H]geranylgeranyl diphosphate, Ras protein, 50 mM HEPES, pH 7.5, 5 mM MgCl_2 , 5 mM dithiothreitol and isoprenyl-
- 15 protein transferase. The FPTase employed in the assay was prepared by recombinant expression as described in Omer, C.A., Kral, A.M., Diehl, R.E., Prendergast, G.C., Powers, S., Allen, C.M., Gibbs, J.B. and Kohl, N.E. (1993) *Biochemistry* 32:5167-5176. The geranylgeranyl-protein transferase-type I employed in the assay was prepared as described in
- 20 U.S. Pat. No. 5,470,832, incorporated by reference. After thermally pre-equilibrating the assay mixture in the absence of enzyme, reactions were initiated by the addition of isoprenyl-protein transferase and stopped at timed intervals (typically 15 min) by the addition of 1 M HCl in ethanol (1 mL). The quenched reactions were allowed to stand for 15
- 25 m (to complete the precipitation process). After adding 2 mL of 100% ethanol, the reactions were vacuum-filtered through Whatman GF/C filters. Filters were washed four times with 2 mL aliquots of 100% ethanol, mixed with scintillation fluid (10 mL) and then counted in a Beckman LS3801scintillation counter.
- 30 For inhibition studies, assays were run as described above, except inhibitors were prepared as concentrated solutions in 100% dimethyl sulfoxide and then diluted 20-fold into the enzyme assay mixture. IC_{50} values were determined with both transferase substrates near K_M concentrations. Nonsaturating substrate conditions for

inhibitor IC₅₀ determinations were as follows: FTase, 650 nM Ras-CVLS, 100 nM farnesyl diphosphate; GGPTase-I, 500 nM Ras-CAIL, 100 nM geranylgeranyl diphosphate.

5 *In vivo* ras prenylation assay

- The cell lines used in this assay consist of either Rat1 or NIH3T3 cells transformed by either viral Ha-*ras*; an N-*ras* chimeric gene in which the C-terminal hypervariable region of v-Ha-*ras* was substituted with the corresponding region from the N-*ras* gene; or
- 10 ras-CVLL, a v-Ha-*ras* mutant in which the C-terminal exon encodes leucine instead of serine, making the encoded protein a substrate for geranylgeranylation by GGPTase I. The assay can also be performed using cell lines transformed with human Ha-*ras*, N-*ras* or Ki4B-*ras*. The assay is performed essentially as described in DeClue, J.E. et al.,
- 15 Cancer Research 51:712-717, (1991). Cells in 10 cm dishes at 50-75% confluency are treated with the test compound(s) (final concentration of solvent, methanol or dimethyl sulfoxide, is 0.1%). After 4 hours at 37°C, the cells are labelled in 3 ml methionine-free DMEM supplemented with 10% regular DMEM, 2% fetal bovine serum,
- 20 400 µCi[³⁵S]methionine (1000 Ci/mmol) and test compound(s). Cells treated with lovastatin, a compound that blocks Ras processing in cells by inhibiting the rate-limiting step in the isoprenoid biosynthetic pathway (Hancock, J.F. et al. *Cell*, 57:1167 (1989); DeClue, J.E. et al. *Cancer Res.*, 51:712 (1991); Sinensky, M. et al. *J. Biol. Chem.*,
- 25 265:19937 (1990)), serve as a positive control in this assay. After an additional 20 hours, the cells are lysed in 1 ml lysis buffer (1% NP40/20 mM HEPES, pH 7.5/5 mM MgCl₂/1mM DTT/10 mg/ml aprotinin/2 mg/ml leupeptin/2 mg/ml antipain/0.5 mM PMSF) and the lysates cleared by centrifugation at 100,000 x g for 45 min. Alternatively, four
- 30 hours after the addition of the labelling media, the media is removed, the cells washed, and 3 ml of media containing the same or a different test compound added. Following an additional 16 hour incubation, the lysis is carried out as above. Aliquots of lysates containing equal numbers of acid-precipitable counts are brought to 1 ml with IP buffer (lysis buffer
- 35 lacking DTT) and immunoprecipitated with the ras-specific monoclonal

antibody Y13-259 (Furth, M.E. et al., J. Virol. 43:294-304, (1982)). Following a 2 hour antibody incubation at 4°C, 200 µl of a 25% suspension of protein A-Sepharose coated with rabbit anti rat IgG is added for 45 min. The immunoprecipitates are washed four times with IP buffer (20 nM HEPES, pH 7.5/1 mM EDTA/1% Triton X-100/0.5% deoxycholate/0.1%/SDS/0.1 M NaCl) boiled in SDS-PAGE sample buffer and loaded on 13% acrylamide gels. When the dye front reached the bottom, the gel is fixed, soaked in Enlightening, dried and autoradiographed. The intensities of the bands corresponding to prenylated and nonprenylated Ras proteins are compared to determine the percent inhibition of prenyl transfer to protein.

In vivo growth inhibition of Ras transformed cells assay

To determine the biological consequences of FPTase inhibition, the effect of the compounds of the instant invention on the anchorage-independent growth of Rat1 cells transformed with either a *v-ras*, *v-raf*, or *v-mos* oncogene is tested. Cell lines transformed with human Ha-ras, N-ras or Ki4B-ras can also be utilized. Cells transformed by v-Raf and v-Mos may be included in the analysis to evaluate the specificity of instant compounds for Ras-induced cell transformation.

Rat 1 cells transformed with either *v-ras*, *v-raf*, or *v-mos* are seeded at a density of 1×10^4 cells per plate (35 mm in diameter) in a 0.3% top agarose layer in medium A (Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum) over a bottom agarose layer (0.6%). Both layers contain 0.1% methanol or an appropriate concentration of the instant compound (dissolved in methanol at 1000 times the final concentration used in the assay). The cells are fed twice weekly with 0.5 ml of medium A containing 0.1% methanol or the concentration of the instant compound. Photomicrographs are taken approximately 16 days after the cultures are seeded and comparisons are made.

In addition, the activity of the compounds of the present invention for treating cancer and/or inhibiting tumor growth is confirmed utilizing the nude mouse tumor xenograft assay described

in Kohl et al., PNAS 91 (1994) 9141-45.

In vitro growth inhibition of human tumor cells assays

- 5 Cancer cells (MCF-7, MDA-468, T47D, MDA-231, SkOv3, A549, SkBr3, PC3, LNCaP or DU-145) are seeded in 6 well clusters at 10,000 or 20,000 cells per well. The growth media utilized in the cell assays is RPMI media [GIBCO], supplemented with 5 or 10% fetal calf serum, glutamine, penicillin and streptomycin. The cell are then treated under one of the following protocols:

10

Protocol A

- After one day in growth media, the cells are exposed to various concentrations of an antineoplastic agent for a four (4) hour period. The cells are then washed twice and placed in a growth media containing a farnesyl-protein transferase inhibitor (FTI) and incubated for 7 to 10 days. At the end of the incubation the cells are harvested by trypsinization and counted in a Coulter counter.

15

Protocol B

- 20 The cells are placed in growth media containing a farnesyl-protein transferase inhibitor (FTI). After one day in the FTI containing growth media, the cells are exposed to various concentrations of a antineoplastic agent for a four (4) hour period. The cells are then washed twice and again placed in a growth media containing a farnesyl-protein transferase inhibitor (FTI) and incubated for 7 to 10 days. At the end of the incubation the cells are harvested by trypsinization and counted in a Coulter counter.

25

Protocol C

- 30 The cells are placed in growth media containing a farnesyl-protein transferase inhibitor (FTI) and various concentrations of a antineoplastic agent. The cells are incubated for 7 to 10 days. At the end of the incubation the cells are harvested by trypsinization and counted in a Coulter counter.

Protocol D-1

The cells are placed in growth media containing a antineoplastic agent at various concentrations for four (4) hours. The monolayer of cells is then separated from the media and washed 4 times with PBS. The cells are trypsinized and counted with a Coulter counter. 20,000 cells are replated on 6 well plates in 0.35% agar over a 0.7% agar layer, both layers which contain vehicle only, 0.2 μ M, 2 μ M or 20 μ M of a farnesyl-protein transferase inhibitor. The cells are fed and treated with the FTI, or vehicle only, twice weekly. At the end of twelve days incubation the cells are scored manually from duplicate wells.

Protocol D-2

The cells are placed in growth media containing a antineoplastic agent for four (4) hours. The monolayer of cells is then separated from the media and washed 4 times with PBS. The cells are trypsinized and counted with a Coulter counter. 10,000 cells are replated on 12 well plates in the standard RPMI media described above which contain vehicle only, 0.2 μ M or 2 μ M of a farnesyl-protein transferase inhibitor. The cells are fed and treated with the FTI, or vehicle only, twice weekly and at those times the colonies are scored manually from duplicate wells. At the end of seven days incubation the cells are scored manually from duplicate wells.

Protocol E-1

Protocol is similar to Protocol A except that the cells are plated at 4,000 to 10,000 cells per well. At the end of 5 days incubation with the FTI, 1 μ L of a 5mg/ml atock of MTT () was added and the cells were incubated an additional 4 hours. The media was then removed and the cells were solubilized with 1 ml isopropanol for 2-3 minutes. The optical density of the cells was then read at 570nm wavelength.

Protocol E-2

Protocol is similar to Protocol B except that the cells are plated at 4,000 to 10,000 cells per well. At the end of 5 days incubation with the FTI, 1 μ L of a 5mg/ml atock of MTT () was added and the cells were incubated an additional 4 hours. The media was then removed and the cells were solubilized with 1 ml isopropanol for 2-3 minutes. The optical density of the cells was then read at 570nm wavelength.

10 Protocol E-3

Protocol is similar to Protocol B except that the cells are plated at 4,000 to 10,000 cells per well. At the end of 5 days incubation with the FTI and the antineoplastic agent, 1 μ L of a 5mg/ml atock of MTT () was added and the cells were incubated an additional 4 hours. The media was then removed and the cells were solubilized with 1 ml isopropanol for 2-3 minutes. The optical density of the cells was then read at 570nm wavelength.

In vitro cell cycle assay

- 20 Cancer cells (MCF-7, MDA-468 or DU-145) are seeded in a 10 cm dish at 1,000,000 cells per dish. After one day in growth media, the cells are exposed to various concentrations of a antineoplastic agent along with vehicle (PBS) or 1 μ M FTI in the vehicle. After 24 hours of exposure to the combination or antineoplastic agent, the cells are trypsinized and stained with ethidium bromide. The stained nuclei are analyzed by flow cytometry for evaluation of the DNA content.

In vivo tumor growth inhibition assay (nude mouse)

- 30 Rodent fibroblasts transformed with oncogenically mutated human Ha-*ras* or Ki-*ras* (10^6 cells/animal in 1 ml of DMEM salts) are injected subcutaneously into the left flank of 8-12 week old female nude mice (Harlan) on day 0. The mice in each oncogene group are randomly assigned to a vehicle, compound or combination treatment group. Animals are dosed subcutaneously starting on day 1 and daily

- for the duration of the experiment. Alternatively, the farnesyl-protein transferase inhibitor may be administered by a continuous infusion pump. Compound, compound combination or vehicle is delivered in a total volume of 0.1 ml. Tumors are excised and weighed when all of the vehicle-treated animals exhibited lesions of 0.5 - 1.0 cm in diameter, typically 11-15 days after the cells were injected. The average weight of the tumors in each treatment group for each cell line is calculated.

- The following dosage groups are utilized to determine the efficacy of the combination of the farnesyl-protein transferase inhibitor (FTI) and antineoplastic agent (agent):
- | | | |
|-------|----|---------------------------------|
| Group | O | Vehicle controls |
| Group | A: | FTI at maximum no effect dose |
| Group | B: | FTI at minimal efficacy dose |
| Group | C: | agent at maximal no effect dose |
| Group | D: | agent at minimal efficacy dose |
| Group | E: | A + C |
| Group | F: | A + D |
| Group | G: | B + C |
| Group | H: | B + D |

Additional doses of FTI and agent can be selected as needed.

WHAT IS CLAIMED IS:

1. A method for achieving a therapeutic effect in a mammal in need thereof which comprises administering to said mammal amounts of at least two therapeutic agents selected from a group consisting of:
- a) a prenyl-protein transferase inhibitor and
 - b) an antineoplastic agent.
2. The method according to Claim 1 wherein an amount of a prenyl-protein transferase inhibitor and an amount of an antineoplastic agent are administered simultaneously.
3. The method according to Claim 1 wherein an amount of an antineoplastic agent and an amount of a prenyl-protein transferase inhibitor are administered consecutively.
4. The method according to Claim 1 wherein the therapeutic effect is treatment of cancer.
5. The method according to Claim 4 wherein the therapeutic effect is selected from inhibition of cancerous tumor growth and regression of cancerous tumors.
6. The method according to Claim 4 wherein the antineoplastic agent is selected from:
- a) a microtubule-stabilising agent;
 - b) a microtubule-disruptor agent;
 - c) an alkylating agent;
 - d) an anti-metabolite;
 - e) epidophyllotoxin;
 - f) an antineoplastic enzyme;
 - g) a topoisomerase inhibitor;

- h) procarbazine;
- i) mitoxantrone;
- j) a platinum coordination complexe;
- k) a biological response modifier;
- 5 l) a growth inhibitor;
- m) a hormonal/antihormonal therapeutic agent and
- n) a haematopoietic growth factor.

7. The method according to Claim 4 wherein the
10 antineoplastic agent is a member of a class of anti-neoplastic agents, said
class selected from: the anthracycline family of drugs, the vinca drugs,
the mitomycins, the bleomycins, the cytotoxic nucleosides, the taxanes,
the epothilones, discodermolide, the pteridine family of drugs, diylenes,
aromatase inhibitors and the podophyllotoxins.

15 8. The method according to Claim 4 wherein the
antineoplastic agent is selected from: paclitaxel, docetaxel, epothilone A,
epothilone B, desoxyepothilone A, desoxyepothilone B, doxorubicin,
carminomycin, daunorubicin, aminopterin, methotrexate, methopterin,
20 dichloro-methotrexate, mitomycin C, porfiromycin, 5-fluorouracil, 6-
mercaptapurine, gemcitabine, cytosine arabinoside, podophyllotoxin,
etoposide, etoposide phosphate, teniposide, melphalan, vinblastine,
vincristine, leurosine, vindesine, leurosine, estramustine, cisplatin,
carboplatin, cyclophosphamide, bleomycin, tamoxifen, ifosamide,
25 melphalan, hexamethyl melamine, thiotepa, cytarabin, idatrexate,
trimetrexate, dacarbazine, L-asparaginase, camptothecin, CPT-11,
topotecan, ara-C, bicalutamide, flutamide, leuprolide, a
pyridobenzoindeole derivative, an interferon and an interleukin.

30 9. The method according to Claim 4 wherein the
antineoplastic agent is selected from: paclitaxel, epothilone A, epothilone
B, desoxyepothilone A, desoxyepothilone B, doxorubicin, daunorubicin,
5-fluorouracil, etoposide, vinblastine, estramustine, cisplatin, ara-C and
bicalutamide.

10. The method according to Claim 4 wherein the prenyl-protein transferase inhibitor is selected from:

- 5 2(S)-Butyl-1-(2,3-diaminoprop-1-yl)-1-(1-naphthoyl)piperazine;
1-(3-Amino-2-(2-naphthylmethylamino)prop-1-yl)-2(S)-butyl-4-(1-naphthoyl)piperazine;
- 10 2(S)-Butyl-1-{5-[1-(2-naphthylmethyl)]-4,5-dihydroimidazol}methyl-4-(1-naphthoyl)piperazine;
1-[5-(1-Benzylimidazol)methyl]-2(S)-butyl-4-(1-naphthoyl)piperazine;
- 15 1-{5-[1-(4-nitrobenzyl)]imidazolymethyl}-2(S)-butyl-4-(1-naphthoyl)piperazine;
1-(3-Acetamidomethylthio-2(R)-aminoprop-1-yl)-2(S)-butyl-4-(1-naphthoyl)piperazine;
- 20 2(S)-Butyl-1-[2-(1-imidazolyl)ethyl]sulfonyl-4-(1-naphthoyl)piperazine;
2(R)-Butyl-1-imidazolyl-4-methyl-4-(1-naphthoyl)piperazine;
- 25 2(S)-Butyl-4-(1-naphthoyl)-1-(3-pyridylmethyl)piperazine;
1-2(S)-butyl-2(R)-(4-nitrobenzyl)amino-3-hydroxypropyl-4-(1-naphthoyl)piperazine;
- 30 1-(2(R)-Amino-3-hydroxyheptadecyl)-2(S)-butyl-4-(1-naphthoyl)-piperazine;
2(S)-Benzyl-1-imidazolyl-4-methyl-4-(1-naphthoyl)piperazine;

- 1-(2(R)-Amino-3-(3-benzylthio)propyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;
- 5 1-(2(R)-Amino-3-[3-(4-nitrobenzylthio)propyl])-2(S)-butyl-4-(1-naphthoyl)piperazine;
- 2(S)-Butyl-1-[(4-imidazolyl)ethyl]-4-(1-naphthoyl)piperazine;
- 2(S)-Butyl-1-[(4-imidazolyl)methyl]-4-(1-naphthoyl)piperazine;
- 10 2(S)-Butyl-1-[(1-naphth-2-ylmethyl)-1H-imidazol-5-yl]acetyl]-4-(1-naphthoyl)piperazine;
- 15 2(S)-Butyl-1-[(1-naphth-2-ylmethyl)-1H-imidazol-5-yl]ethyl]-4-(1-naphthoyl)piperazine;
- 1-(2(R)-Amino-3-hydroxypropyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;
- 1-(2(R)-Amino-4-hydroxybutyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;
- 20 1-(2-Amino-3-(2-benzyloxyphenyl)propyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;
- 1-(2-Amino-3-(2-hydroxyphenyl)propyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;
- 25 1-[3-(4-imidazolyl)propyl]-2(S)-butyl-4-(1-naphthoyl)-piperazine;
- 2(S)-*n*-Butyl-4-(2,3-dimethylphenyl)-1-(4-imidazolylmethyl)-piperazin-5-one;
- 30 2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-4-(2,3-dimethylphenyl)piperazin-5-one;

- 1-[1-(4-Cyanobenzyl)imidazol-5-ylmethyl]-4-(2,3-dimethylphenyl)-
2(S)-(2-methoxyethyl)piperazin-5-one;
- 5 2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(1-naphthylmethyl)imidazol-5-
ylmethyl]-piperazine;
- 2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(2-naphthylmethyl)imidazol-5-
ylmethyl]-piperazine;
- 10 2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-4-(1-
naphthoyl)piperazine;
- 2(S)-*n*-Butyl-1-[1-(4-methoxybenzyl)imidazol-5-ylmethyl]-4-(1-
naphthoyl)piperazine;
- 15 2(S)-*n*-Butyl-1-[1-(3-methyl-2-butenyl)imidazol-5-ylmethyl]-4-(1-
naphthoyl)piperazine;
- 2(S)-*n*-Butyl-1-[1-(4-fluorobenzyl)imidazol-5-ylmethyl]-4-(1-
naphthoyl)piperazine;
- 20 2(S)-*n*-Butyl-1-[1-(4-chlorobenzyl)imidazol-5-ylmethyl]-4-(1-
naphthoyl)piperazine;
- 25 1-[1-(4-Bromobenzyl)imidazol-5-ylmethyl]-2(S)-*n*-butyl-4-(1-
naphthoyl)piperazine;
- 2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(4-trifluoromethylbenzyl)imidazol-
5-ylmethyl]-piperazine;
- 30 2(S)-*n*-Butyl-1-[1-(4-methylbenzyl)imidazol-5-ylmethyl]-4-(1-
naphthoyl)piperazine;

- 2(S)-*n*-Butyl-1-[1-(3-methylbenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)-piperazine;
- 5 1-[1-(4-Phenylbenzyl)imidazol-5-ylmethyl]-2(S)-*n*-butyl-4-(1-naphthoyl)-piperazine;
- 2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(2-phenylethyl)imidazol-5-ylmethyl]-piperazine;
- 10 2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(4-trifluoromethoxy)imidazol-5-ylmethyl]piperazine;
- 1 1-[[1-(4-cyanobenzyl)-1H-imidazol-5-yl]acetyl]-2(S)-*n*-butyl-4-(1-naphthoyl)piperazine;
- 15 (S)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(methanesulfonyl)ethyl]-2-piperazinone;
- 20 (S)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)ethyl]-2-piperazinone;
- (R)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)methyl]-2-piperazinone;
- 25 (S)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[N-ethyl-2-acetamido]-2-piperazinone;
- (±)-5-(2-Butynyl)-1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone;
- 30 1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone;
- 5(S)-Butyl-4-[1-(4-cyanobenzyl-2-methyl)-5-imidazolylmethyl]-1-(2,3-dimethylphenyl)-piperazin-2-one;
- 35

- 4-[1-(2-(4-Cyanophenyl)-2-propyl)-5-imidazolylmethyl]-1-(3-chlorophenyl)-5(S)-(2-methylsulfonylethyl)piperazin-2-one;
- 5 (S)-n-Butyl-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-1-(2-methylphenyl)piperazin-2-one;
- 4-[1-(4-Cyanobenzyl)-5-imidazolylmethyl]-5(S)-(2-fluoroethyl)-1-(3-chlorophenyl)piperazin-2-one;
- 10 4-[3-(4-Cyanobenzyl)pyridin-4-yl]-1-(3-chlorophenyl)-5(S)-(2-methylsulfonylethyl)-piperazin-2-one;
- 4-[5-(4-Cyanobenzyl)-1-imidazolylethyl]-1-(3-chlorophenyl)piperazin-2-one;
- 15 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-homoserine lactone,
- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-homoserine,
- 20 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-2-methyl-3-phenylpropionyl-homoserine lactone,
- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-2-methyl-3-phenylpropionyl-homoserine,
- 25 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-4-pentenoyl-homoserine lactone,
- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-pentyloxy-4-pentenoyl-homoserine,
- 30 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-pentyloxy-4-pentenoyl-homoserine,
- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxypentanoyl-homoserine lactone,
- 35

- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentylloxypentanoyl-homoserine,
- 5 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]5-pentylloxy-4-methylpentanoyl-homoserine lactone,
- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentylloxy-4-methylpentanoyl-homoserine,
- 10 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentylloxy-3-methylbutanoyl-homoserine lactone,
- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentylloxy-3-methylbutanoyl-homoserine,
- 15 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentylloxy-3-phenylbutanoyl-homoserine lactone,
- 20 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentylloxy-3-phenylbutanoyl-homoserine,
- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentylthio-2-methyl-3-phenylpropionyl-homoserine lactone,
- 25 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentylthio-2-methyl-3-phenylpropionyl-homoserine,
- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentylsulfonyl-2-methyl-3-phenylpropionyl-homoserine lactone,
- 30 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentylsulfonyl-2-methyl-3-phenylpropionyl-homoserine,
- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-

- pentylxy-3-phenylpropionyl-methionine methyl ester,
- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentylxy-3-phenylpropionyl-methionine,
- 5 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentylxy-3-phenylpropionyl-methionine sulfone methyl ester,
- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentylxy-3-phenylpropionyl-methionine sulfone (Compound 6),
- 10 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentylxy-3-phenylpropionyl-methionine sulfone isopropyl ester,
- 15 2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentylxy-3-naphth-2-yl-propionyl-methionine sulfone methyl ester,
- 2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentylxy-3-naphth-2-yl-propionyl-methionine sulfone,
- 20 2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentylxy-3-naphth-1-yl-propionyl-methionine sulfone methyl ester,
- 25 2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentylxy-3-naphth-1-yl-propionyl-methionine sulfone,
- 2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentylxy-3-methylbutanoyl-methionine methyl ester.
- 30 2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentylxy-3-methylbutanoyl-methionine,

Disulphide of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)methyl]pentylloxy-3-phenylpropionyl-homoserine lactone,

- 5 Disulphide of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentylloxy-3-phenylpropionyl-homoserine,

Disulphide of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)methyl]pentylloxy-3-methylbutanoyl-methionine methyl ester

- 10 1-(4-Biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(4-Cyanobenzyl)-5-(4'-phenylbenzamido)ethyl-imidazole

- 15 1-(2'-Trifluoromethyl-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(4-Biphenylethyl)-5-(4-cyanobenzyl)imidazole

- 20 1-(2'-Bromo-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(2'-Methyl-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

- 25 1-(2'-Trifluoromethoxy-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

- 30 1-(4-(3',5'-dichloro)-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(2'-Methoxy-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

- 1-(2'-Chloro-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole
- 5 1-(2-Chloro-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole
- 1-(3-Chloro-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole
- 10 1-(4-(3',5'-Bis-trifluoromethyl)-biphenylmethyl)-5-(4-cyanobenzyl) imidazole
- 15 1-(2'-Trifluoromethyl-4-biphenylmethyl)-5-(4-cyanobenzyl)-4-methylimidazole
- 1-(4-Biphenylmethyl)-5-(4-cyanophenyl)-imidazole
- 20 5-(4-Cyanophenyl)-1-(2'-methyl-4-biphenylmethyl)-imidazole
- 5-(4-Biphenyl)-1-(4-cyanobenzyl)-imidazole
- 25 5-(2'-Methyl-4-biphenyl)-1-(4-cyanobenzyl)-imidazole
- 30 5-(4-(3',5'-dichloro)biphenylmethyl)-1-(4-cyanobenzyl)imidazole
- 1-(4-biphenylmethyl)-5-(1-(R,S)-acetoxy-1-(4-cyanophenyl)methyl)imidazole
- 35

1-(4-Biphenylmethyl)-5-(1-(R,S)-hydroxy-1-(4-cyanophenyl)
methylimidazole

5

1-(4-Biphenylmethyl)-5-(1-(R,S)-amino-1-(4-cyanophenyl)
methylimidazole

10 1-(4-biphenylmethyl)-5-(1-(R,S)-methoxy-1-(4-cyanophenyl)-
methylimidazole

15

1-(4-Cyanobenzyl)-5-(1-hydroxy-1-(4-biphenyl)-methyl imidazole

1-(4-Cyanobenzyl)-5-(1-oxo-1-(4-biphenyl)-methyl imidazole

20

1-(4-Cyanobenzyl)-5-(1-hydroxy-1-(3-fluoro-4-biphenyl)-methyl)-
imidazole

1-(4-Cyanobenzyl)-5-(1-hydroxy-1-(3-biphenyl)methyl-imidazole

25

5-(2-[1,1'-Biphenyl]vinylene)-1-(4-cyanobenzyl)imidazole

1-[N-(1-(4-cyanobenzyl)-5-imidazolylmethyl)amino]-3-methoxy-4-
phenylbenzene

30

1-(4-Biphenylmethyl)-5-(4-bromophenyl)-imidazole

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1-(3'-Methyl-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(4'-Methyl-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

5 1-(3'-Trifluoromethyl-4-biphenylmethyl)-5-(4-cyanobenzyl)
imidazole

10 1-(4'-Trifluoromethyl-4-biphenylmethyl)-5-(4-cyanobenzyl)
imidazole

1-(3'-Chloro-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

15 1-(4'-Chloro-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(2'3'-Dichloro-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

20 1-(2'4'-Dichloro-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

25 1-(2'5'-Dichloro-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(3'-Trifluoromethoxy-4-biphenylmethyl)-5-(4-cyanobenzyl)
imidazole

30 1-(2'-Fluoro-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

- 1-(4-(2'-Trifluoromethylphenyl)-2-Chlorophenylmethyl)-5-(4-cyanobenzyl) imidazole
- 5 1-{1-(4-(2'-trifluoromethylphenyl)phenyl)ethyl}-5-(4-cyanobenzyl) imidazole
- 10 1-(2'-Trifluoromethyl-4-biphenylpropyl)-5-(4-cyanobenzyl) imidazole
- 15 1-(2'-N-t-Butoxycarbonylamino-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole
- 1-(2'-Acetylaminoethyl-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole
- 20 1-(2'-Methylsulfonylaminoethyl-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole
- 1-(2'-Ethylaminoethyl-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole
- 25 1-(2'-Phenylaminoethyl-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole
- 1-(2'-Glycylaminoethyl-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole
- 30 1-(2'-Methyl-4-biphenylmethyl)-2-chloro-5-(4-cyanobenzyl) imidazole

- 1-(2'-Methyl-4-biphenylmethyl)- 4-chloro 5-(4-cyanobenzyl)
imidazole
- 5 1-(3'-Chloro-2-methyl-4-biphenylmethyl)-4-(4-
cyanobenzyl)imidazole
- 10 1-(3'-Chloro-2-methyl-4-biphenylmethyl)-5-(4-
cyanobenzyl)imidazole
- 15 1-(3'-Trifluoromethyl-2-methyl-4-biphenylmethyl)-4-(4-
cyanobenzyl) imidazole
- 20 1-(3'-Methoxy-2-methyl-4-biphenylmethyl)-5-(4-
cyanobenzyl)imidazole
- 25 1-(2'-Chloro-4'-fluoro-4-biphenylmethyl)-5-(4-
cyanobenzyl)imidazole
- 30 1-(2'-Ethyl-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole
- 1-(2'-(2-Propyl)-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole
- 1-(2'-(2-Methyl-2-propyl)-4-biphenylmethyl)-5-(4-
cyanobenzyl)imidazole

- 1-(2'-Ethyl-4-biphenylmethyl)-5-(4-(1*H*-tetrazol-5-yl))benzyl)imidazole
- 5
- 1-[1-(4-Cyanobenzyl)imidazol-5-ylmethoxy]-4-(2'-methylphenyl)-2-(3-*N*-phthalimido-1-propyl)benzene
- 10
- 1-(3',5'-Ditrifluoromethyl-2-methyl-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole
- 15
- 1-(3',5'-Chloro-2-methyl-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole
- 20
- 1-(3',5'-Dimethyl-2-methyl-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole
- 25
- 1-(3-(*N*-Boc-aminomethyl)-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole
- 30
- 1-(4-Cyanobenzyl)-2-methyl-5-(2'-methylbiphenyl-4-yl)oxy)imidazole

5-(4-Cyanobenzyl)-1-(3-cyano-2'-trifluoromethylbiphenyl-4-ylmethyl)-imidazole

5 2-Amino-5-(biphenyl-4-ylmethyl)-1-(4-cyanobenzyl)imidazole

2-Amino-1-(biphenyl-4-ylmethyl)-5-(4-cyanobenzyl)imidazole

10

1-(3-Butylbiphenyl-4-ylmethyl)-5-(4-cyanobenzyl)-imidazole

1-(3-Propylbiphenyl-4-ylmethyl)-5-(4-cyanobenzyl)-imidazole

15

1-(4-Biphenylmethyl)-4-(4-cyanobenzyl-2-methylimidazole

20 1-(4-Cyanobenzyl)-5-[(3-fluoro-4-biphenyl)methyl]imidazole

1-(4-Cyanobenzyl)-5-[1-(4-biphenyl)-1-hydroxy]ethyl-2-methylimidazole

25

1-(4-Cyanobenzyl)-5-(4-biphenylmethyl)-2-methylimidazole

30 1-(4-Cyanobenzyl)-5-[1-(4-biphenyl)]ethyl-2-methyl imidazole

1-(4-Cyanobenzyl)-5-[1-(4-biphenyl)]vinylidene-2-methylimidazole
and

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- 1-(4-Cyanobenzyl)-5-[2-(4-biphenyl)]vinylene-2-methylimidazole
- 5 1-(4-[Pyrid-2-yl]phenylmethyl)-5-(4-cyanobenzyl)imidazole
- 1-(4-[3-Methylpyrazin-2-yl]phenylmethyl)-5-(4-cyanobenzyl)imidazole
- 10 1-(4-(Pyrimidinyl-5-yl)phenylmethyl)-5-(4-cyanobenzyl)imidazole
- 1-(2-Phenylpyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole
- 15 1-(2-Phenyl-N-Oxopyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole
- 1-(3-Phenylpyrid-6-ylmethyl)-5-(4-cyanobenzyl)imidazole
- 1-(3-Phenyl-N-Oxopyrid-6-ylmethyl)-5-(4-cyanobenzyl)imidazole
- 20 1-(2-(3-Trifluoromethoxyphenyl)-pyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole
- 1-(2-(2-Trifluoromethylphenyl)-pyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole
- 25 1-(3-Phenyl-2-Chloropyrid-6-ylmethyl)-5-(4-cyanobenzyl)imidazole
- 1-(3-Phenyl-4-chloropyrid-6-ylmethyl)-5-(4-cyanobenzyl)imidazole
- 30 1-(2-Amino-3-phenylpyrid-6-ylmethyl)-5-(4-cyanobenzyl)imidazole
- 1-(2-[Pyrid-2-yl]pyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole
- N-{ 1-(4-Cyanobenzyl)-1H-imidazol-5-yl)methyl }-5-(pyrid-2-yl)-2-amino-pyrimidine
- 35 *N,N*-bis(4-Imidazolemethyl)amino-3-[(3-carboxyphenyl)oxy]benzene

- N,N*-bis(4-Imidazolemethyl)amino-4-[(3-carboxyphenyl)oxy]benzene
- 5 *N,N*-bis(4-Imidazolemethyl)amino-3-[(3-carbomethoxyphenyl)-oxy]benzene
- N,N*-bis(4-Imidazolemethyl)amino-4-[(3-carbomethoxyphenyl)-oxy]benzene
- 10 *N*-(4-Imidazolemethyl)-*N*-(4-nitrobenzyl)aminomethyl-3-[(3-carboxyphenyl)oxy]benzene
- N*-(4-Imidazolemethyl)-*N*-(4-nitrobenzyl)aminomethyl-3-[(3-carbomethoxyphenyl)oxy]benzene
- 15 *N*-(4-Imidazolemethyl)-*N*-(4-nitrobenzyl)amino-3-(phenoxy)benzene
- N*-(4-Imidazolemethyl)-*N*-(4-nitrobenzyl)amino-4-(phenoxy)benzene
- 20 *N*-(4-Imidazolemethyl)-*N*-(4-nitrobenzyl)amino-4-(phenylthio)benzene
- N*-Butyl-*N*-[1-(4-cyanobenzyl)-5-imidazolemethyl]amino-4-(phenoxy)benzene
- 25 *N*-[1-(4-Cyanobenzyl)-5-imidazolemethyl]amino-4-(phenoxy)benzene
- N*-(4-Imidazolemethyl)amino-3-[(3-carboxyphenyl)oxy]benzene
- 30 1-[*N*-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-*N*-(4-cyanobenzyl)amino]-4-(phenoxy)benzene
- (±)-4-[(4-imidazolylmethyl)amino]pentyl-1-(phenoxy)benzene
- 1-[(*N*-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-*N*-(n-butyl)amino)methyl]-4-(phenoxy)benzene
- 35

- 4-[N-(1-(4-cyanobenzyl)-5-imidazolymethyl)-N-(n-butyl)amino]-1-(phenylthio)benzene
- 5 (±)-4-[N-(1-(4-cyanobenzyl)-4-imidazolymethyl)-N-(n-butyl)amino]-1-(phenylsulfinyl)benzene
- 3-[N-(4-imidazolymethyl)-N-(n-butyl)amino]-N-(phenyl)benzenesulfonamide and
- 10 1-[N-(1-(4-cyanobenzyl)-5-imidazolymethyl)amino]-3-methoxy-4-phenylbenzene
- 4-{3-[4-(2-Oxo-2-H-pyridin-1-yl)benzyl]-3-H-imidazol-4-ylmethyl}benzonitrile
- 15 4-{3-[4-(2-Oxo-2-H-pyridin-1-yl)benzyl]-3-H-imidazol-4-ylmethyl}benzonitrile
- 20 4-{3-[4-(2-Oxo-piperidin-1-yl)benzyl]-3-H-imidazol-4-ylmethyl}benzonitrile
- 4-{3-[3-Methyl-4-(2-oxopiperidin-1-yl)-benzyl]-3-H-imidazol-4-ylmethyl}-benzonitrile
- 25 (4-{3-[4-(2-Oxo-pyrrolidin-1-yl)-benzyl]-3H-imidazol-4-ylmethyl}-benzonitrile
- 4-{3-[4-(3-Methyl-2-oxo-2-H-pyrazin-1-yl)-benzyl]-3-H-imidazol-4-ylmethyl}-benzonitrile
- 30 4-{3-[2-Methoxy-4-(2-oxo-2-H-pyridin-1-yl)-benzyl]-3-H-imidazol-4-ylmethyl}-benzonitrile
- 35 4-{1-[4-(5-Chloro-2-oxo-2H-pyridin-1-yl)-benzyl]-1H-pyrrol-2-ylmethyl}-benzonitrile

4-[1-(2-Oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-pyrrol-2-ylmethyl]-benzonitrile

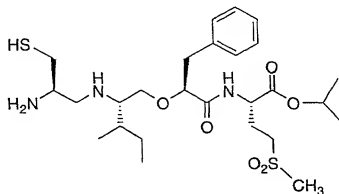
- 5 4-[1-(5-Chloro-2-oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-pyrrol-2-ylmethyl]-benzonitrile
 4-[3-(2-Oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl]benzonitrile
- 10 4-{3-[1-(3-Chloro-phenyl)-2-oxo-1,2-dihydropyridin-4-ylmethyl]-3H-imidazol-4-ylmethyl}benzonitrile

or a pharmaceutically acceptable salt, disulfide or optical isomer thereof.

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11. The method according to Claim 4 wherein the prenyl-protein transferase inhibitor is selected from:

- 20 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone isopropyl ester (Compound A)



- 25 1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone;

(R)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)methyl]-2-piperazinone;

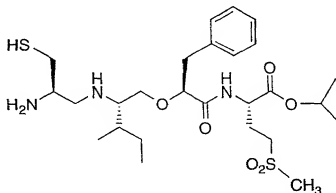
- 4-[1-(5-Chloro-2-oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-pyrrol-2-ylmethyl]-benzonitrile and

1-[N-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-N-(4-cyanobenzyl)amino]-4-(phenoxy)benzene

- 10 or a pharmaceutically acceptable salt, disulfide or optical isomer thereof.

12. The method according to Claim 4 wherein the antineoplastic agent is paclitaxel and the prenyl-protein transferase inhibitor is

2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone isopropyl ester (Compound A)



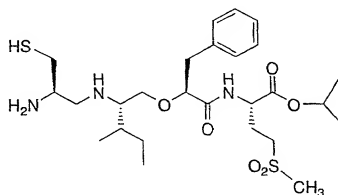
- 20 13. A method of treating cancer in a mammal in need thereof which comprises administering to said mammal amounts of a prenyl-protein transferase inhibitor and applying to the mammal radiation therapy.

14. The method according to Claim 13 wherein the amount of a prenyl-protein transferase inhibitor and the radiation therapy are administered simultaneously.

5 15. The method according to Claim 13 wherein the amount of a prenyl-protein transferase inhibitor is administered first and the radiation therapy is administered after the prenyl-protein transferase inhibitor has been administered.

10 16. The method according to Claim 13 wherein the prenyl-protein transferase inhibitor is selected from:

2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-
3(S)-methyl]-pentyl-3-phenylpropionyl-methionine sulfone
15 isopropyl ester (Compound A)



1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazine;

20 (R)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)methyl]-2-piperazine;

4-[1-(5-Chloro-2-oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-pyrrol-2-ylmethyl]-benzonitrile and

25

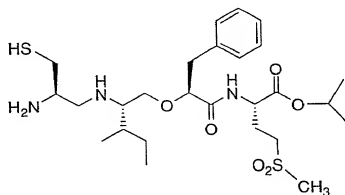
1-[N-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-N-(4-cyanobenzyl)amino]-4-(phenoxy)benzene

or a pharmaceutically acceptable salt, disulfide or optical isomer thereof.

5

17. The method according to Claim 13 wherein the prenyl-protein transferase inhibitor is selected from:

- 10 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone isopropyl ester (Compound A)



- 15 or a pharmaceutically acceptable salt, disulfide or optical isomer thereof.

18. The method according to Claim 13 wherein the prenyl-protein transferase inhibitor is:

20

1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone;

or a pharmaceutically acceptable salt thereof.

25

19. The method according to Claim 13 wherein the prenyl-protein transferase inhibitor is selected from:

(R)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-
5 [2-(ethanesulfonyl)methyl]-2-piperazinone;

or a pharmaceutically acceptable salt or optical isomer thereof.

20. The method according to Claim 13 wherein the prenyl-protein transferase inhibitor is selected from:

4-[1-(5-Chloro-2-oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-pyrrol-2-ylmethyl]-benzonitrile and

15 or a pharmaceutically acceptable salt thereof.

21. The method according to Claim 13 wherein the prenyl-protein transferase inhibitor is selected from:

20 1-[N-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-N-(4-cyanobenzyl)amino]-4-(phenoxy)benzene

or a pharmaceutically acceptable salt thereof.

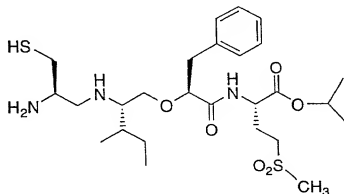
25 22. The method according to Claim 13 which additionally comprises administering to the mammal an amount of an antineoplastic agent.

30 23. The method according to Claim 22 wherein the amount of a prenyl-protein transferase inhibitor and the amount of an antineoplastic agent are administered simultaneously.

35 24. The method according to Claim 22 wherein the amount of an antineoplastic agent and the amount of a prenyl-protein transferase inhibitor are administered consecutively.

25. The method according to Claim 22 wherein the prenyl-protein transferase inhibitor is selected from:

- 5 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone isopropyl ester (Compound A)



- 10 1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolymethyl]-2-piperazinone;
 (R)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolymethyl]-5-[2-(ethanesulfonyl)methyl]-2-piperazinone;
 15 4-[1-(5-Chloro-2-oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-pyrrol-2-ylmethyl]-benzonitrile and
 1-[N-(1-(4-cyanobenzyl)-5-imidazolymethyl)-N-(4-cyanobenzyl)amino]-4-(phenoxy)benzene
 20

or a pharmaceutically acceptable salt, disulfide or optical isomer thereof.

- 25 26. A pharmaceutical composition for achieving a therapeutic effect in a mammal in need thereof which comprises

amounts of at least two therapeutic agents selected from a group consisting of:

- a prenyl-protein transferase inhibitor and
- an antineoplastic agent.

5

27. The pharmaceutical composition according to Claim 26 comprising an amount of a prenyl-protein transferase inhibitor and an amount of an antineoplastic agent.

10

28. The pharmaceutical composition according to Claim 26 wherein the therapeutic effect is treatment of cancer.

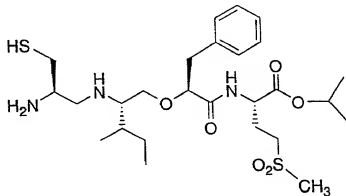
15

29. The pharmaceutical composition according to Claim 26 wherein the therapeutic effect is selected from inhibition of cancerous tumor growth and the regression of cancerous tumors.

20

30. The composition according to Claim 27 wherein the antineoplastic agent is paclitaxel and the prenyl-protein transferase inhibitor is

2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone isopropyl ester (Compound A)



31. A method of preparing a pharmaceutical composition
25 for achieving a therapeutic effect in a mammal in need thereof which

comprises mixing amounts of at least two therapeutic agents selected from a group consisting of:

- 5 a) a prenyl-protein transferase inhibitor and
 b) an antineoplastic agent.

32. The method of preparing a pharmaceutical composition according to Claim 26 comprising mixing an amount of a prenyl-protein transferase inhibitor and an amount of an antineoplastic agent.

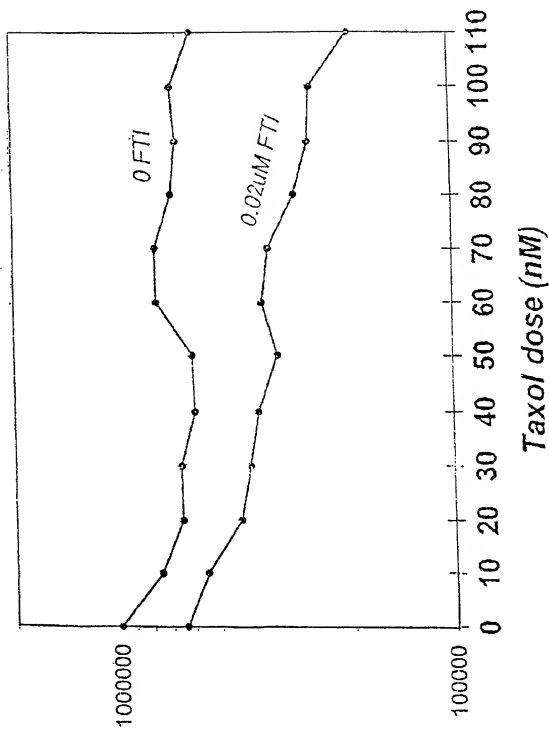


Figure 1

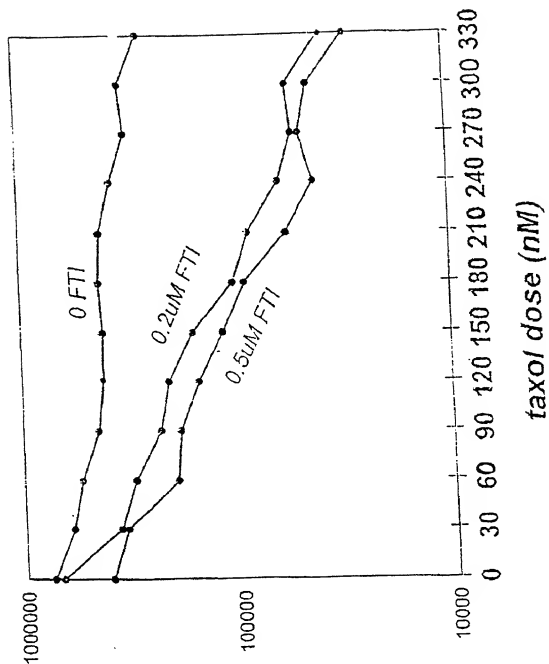


Figure 2

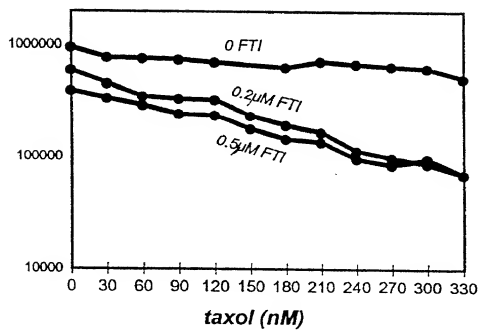
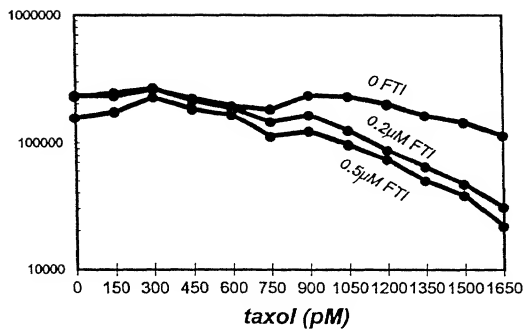


Fig. 2A

**Fig. 2B**

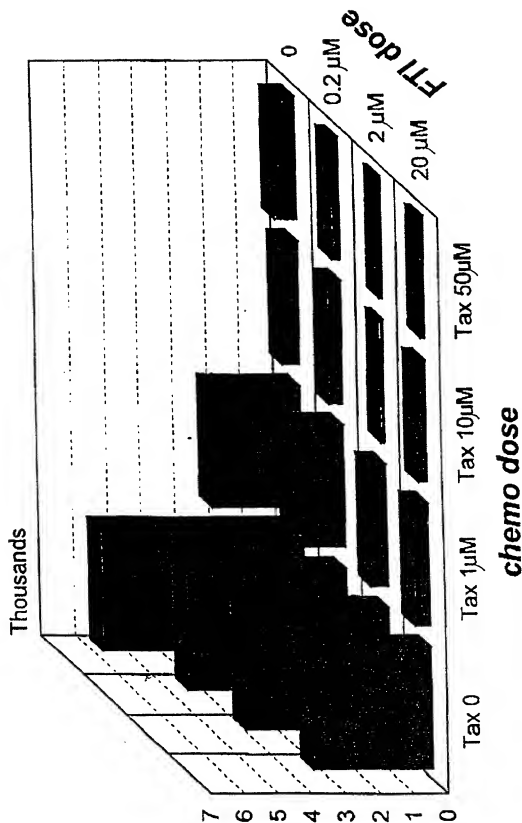


Figure 3A

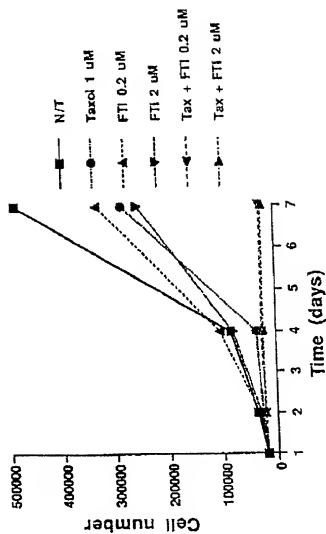


Figure 3B

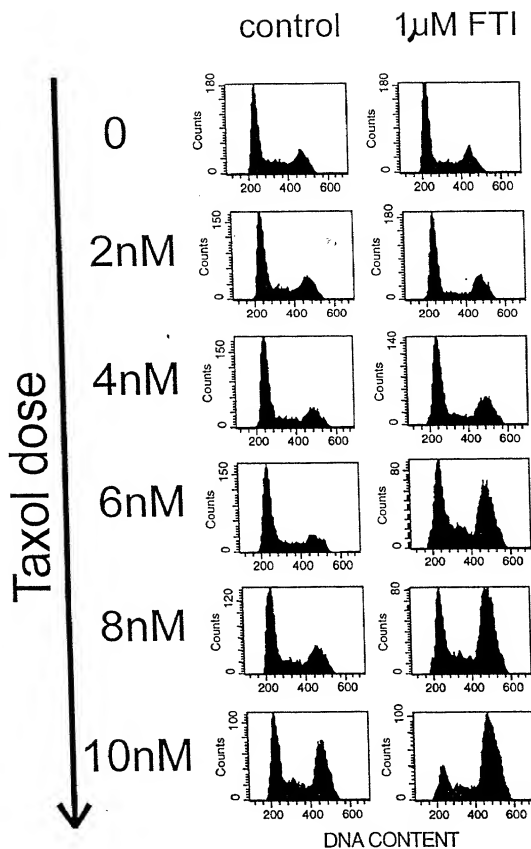


Figure 4

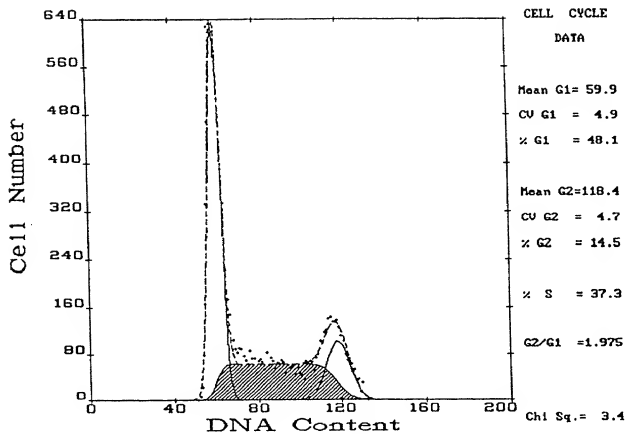


Figure 4A

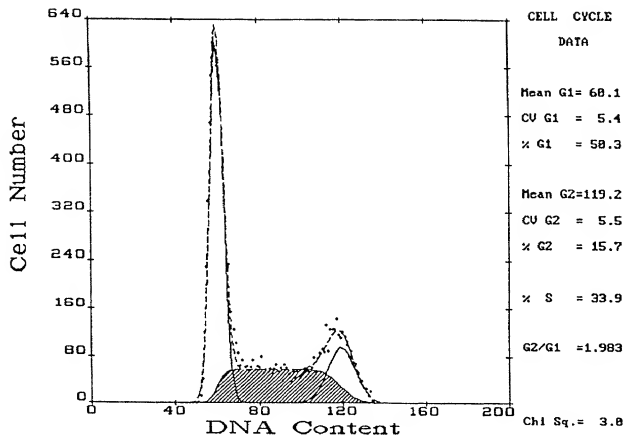


Figure 4B

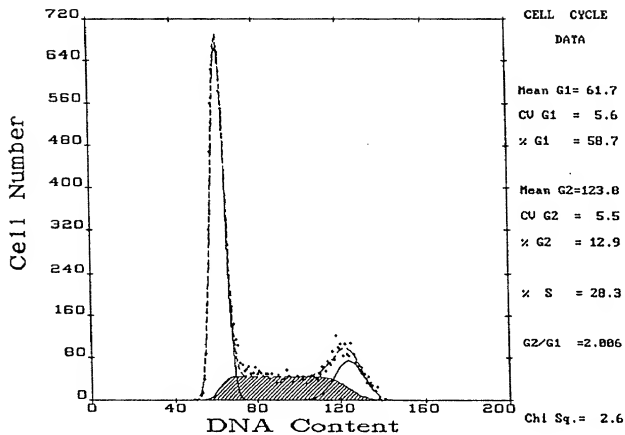


Figure 4C

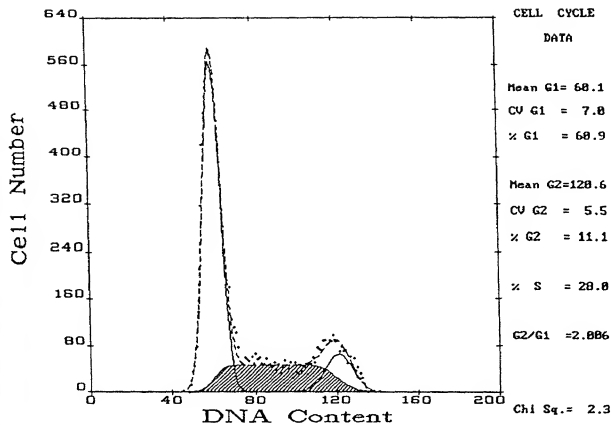


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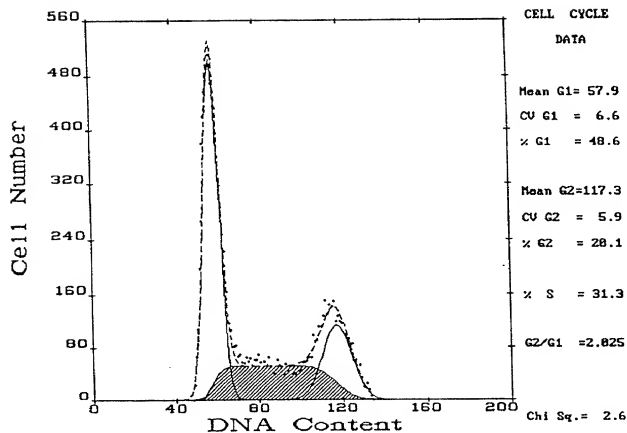


Figure 4E

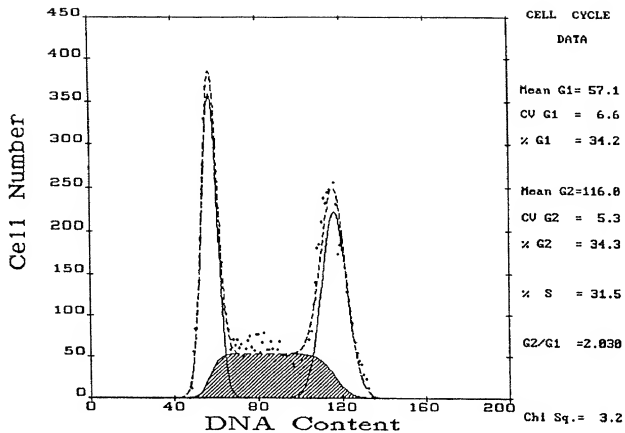


Figure 4F

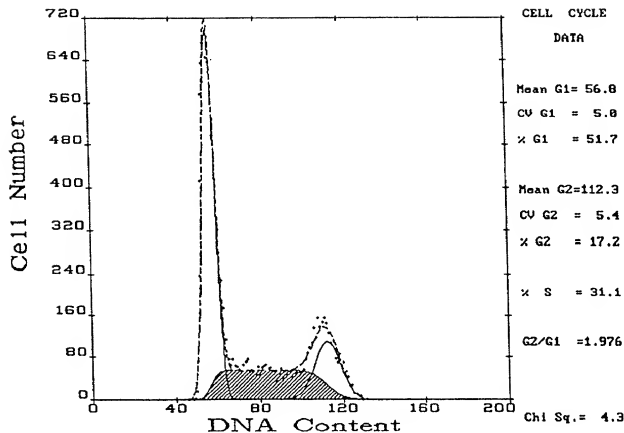


Figure 4G

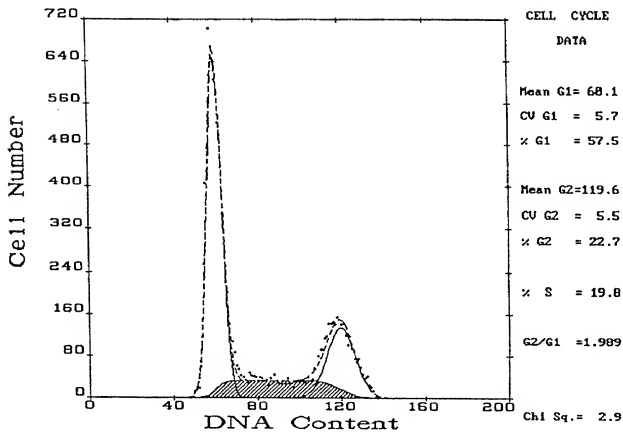


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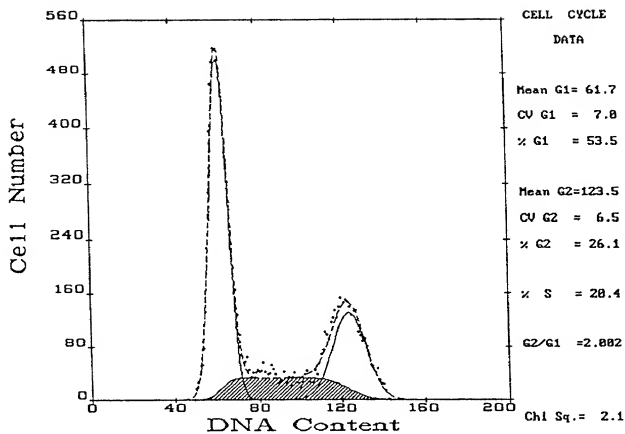


Figure 4I

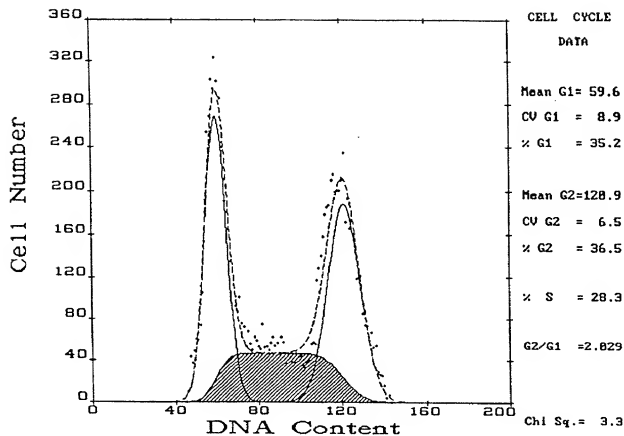


Figure 4J

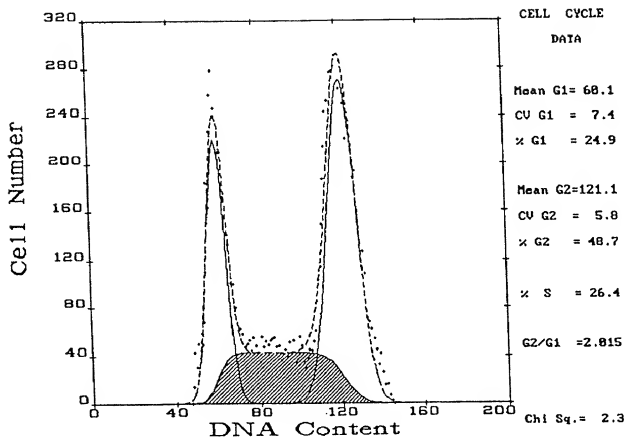


Figure 4K

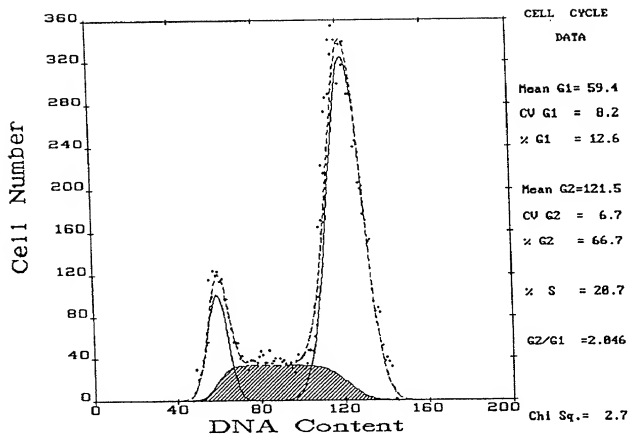
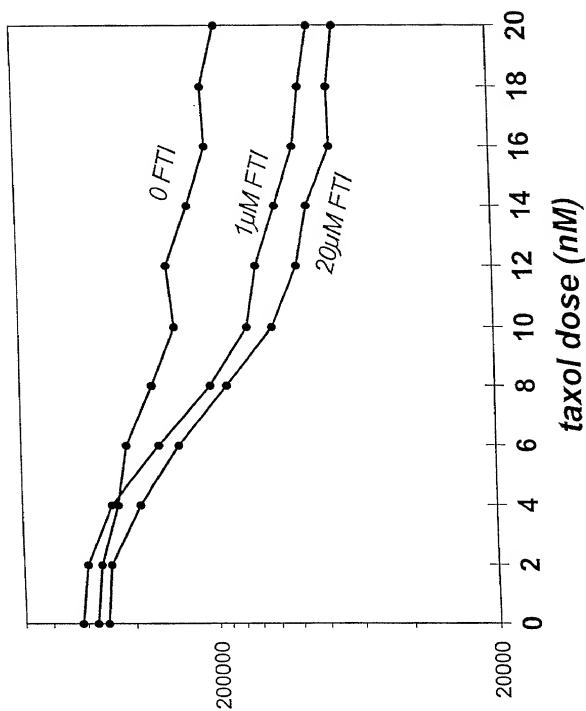


Figure 4L

	control	1 μ M FTI
taxol dose		
4nM	3.3%	12.3%
6nM	8.8%	16.9%
8nM	20.5%	27.6%
10nM	30.0%	36.0%

Figure 5

Fig. 6



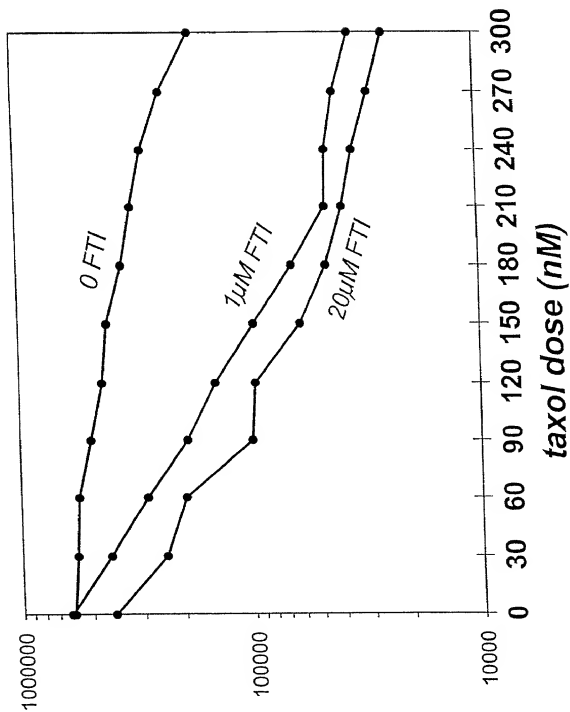


Fig. 7

Fig. 8

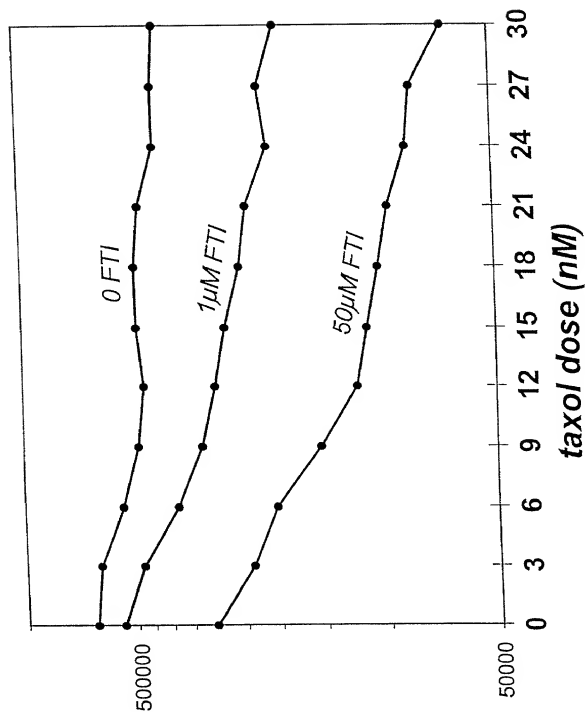


Fig. 9

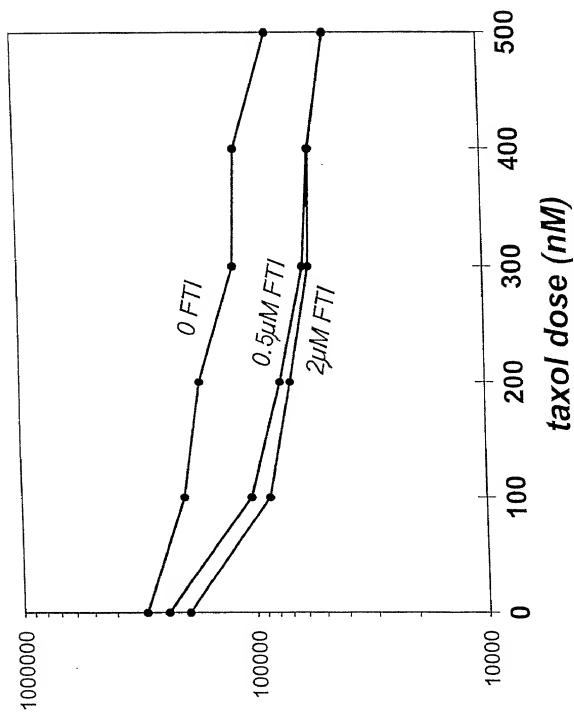


Fig. 10

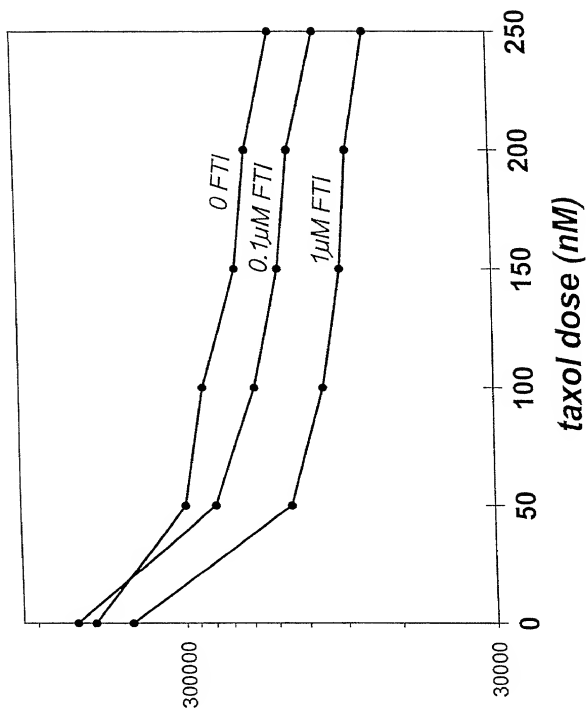


Fig. 11

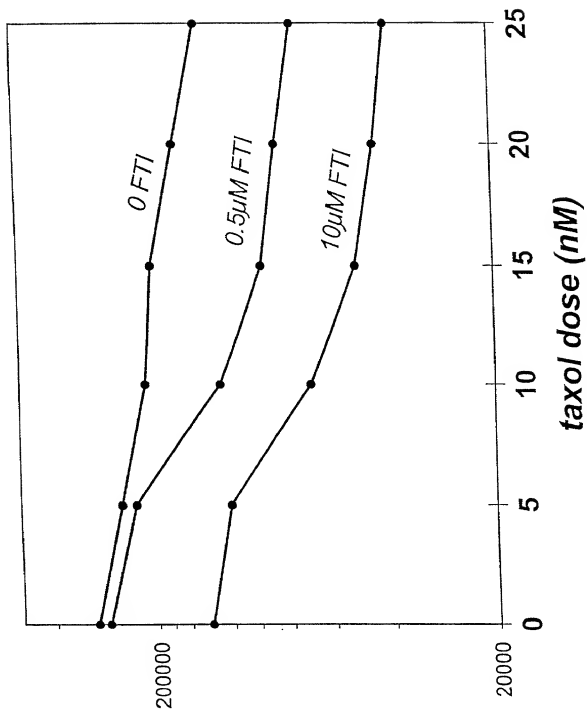


Fig. 12

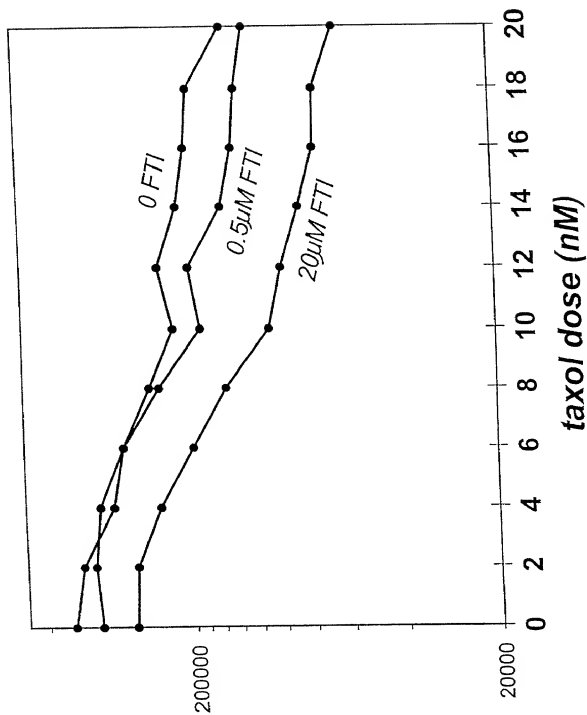
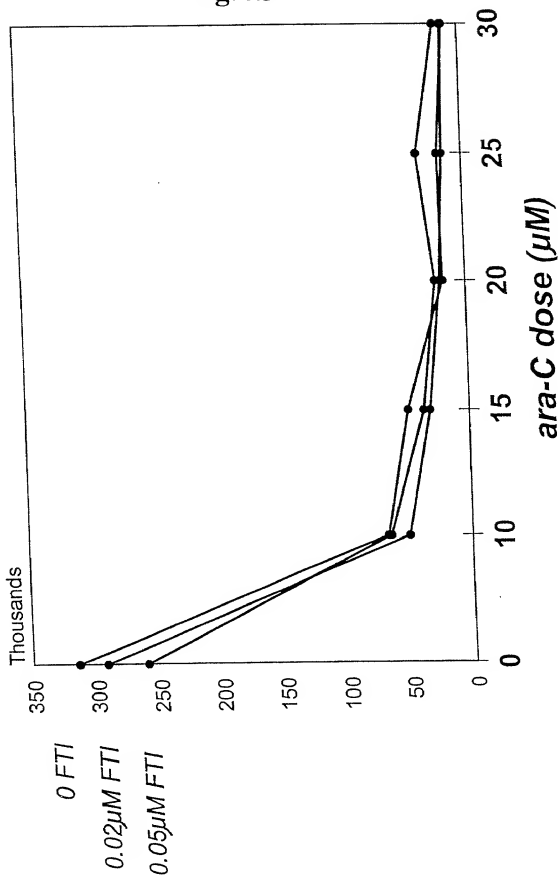


Fig. 13



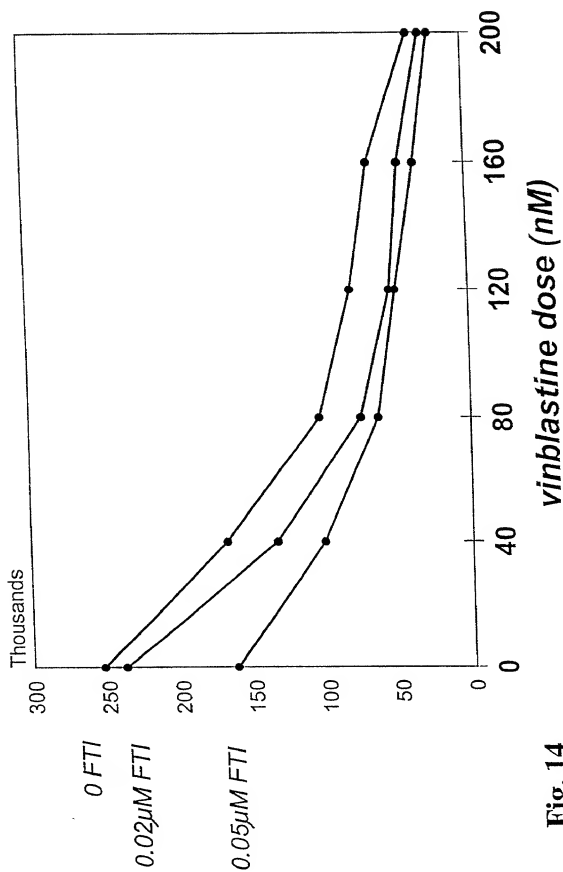


Fig. 14

Fig. 15

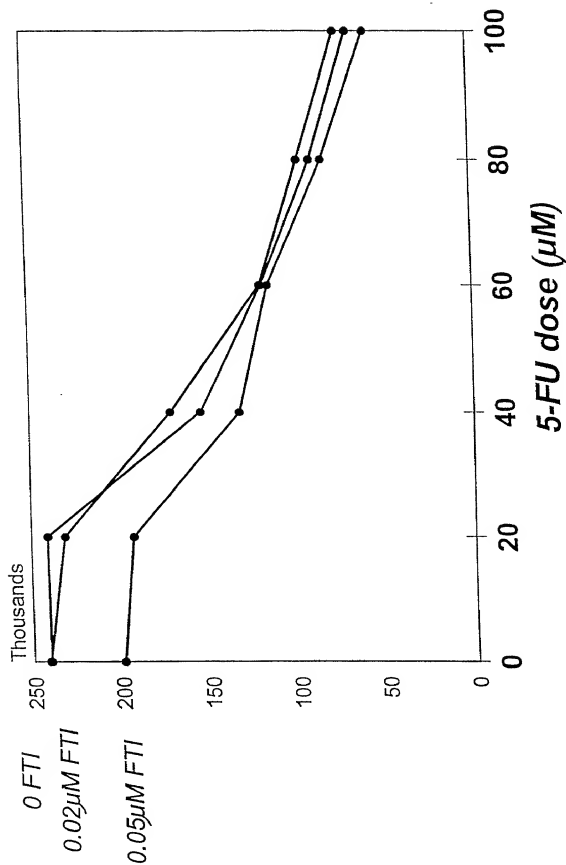


Fig. 16

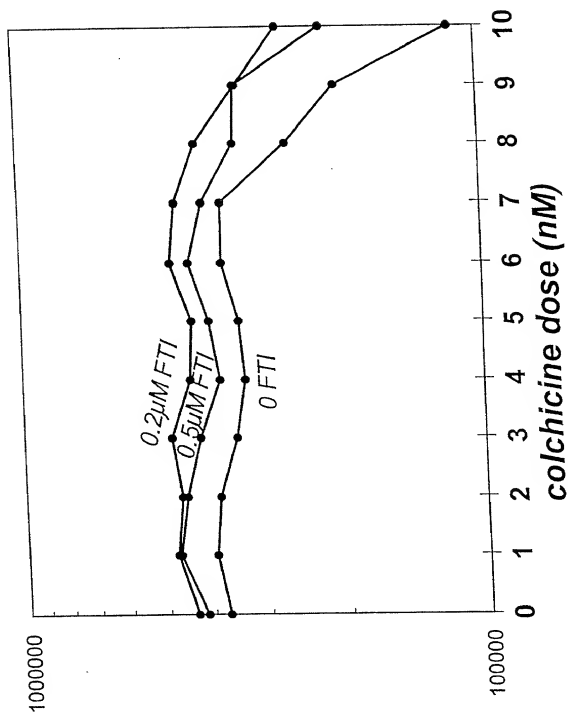
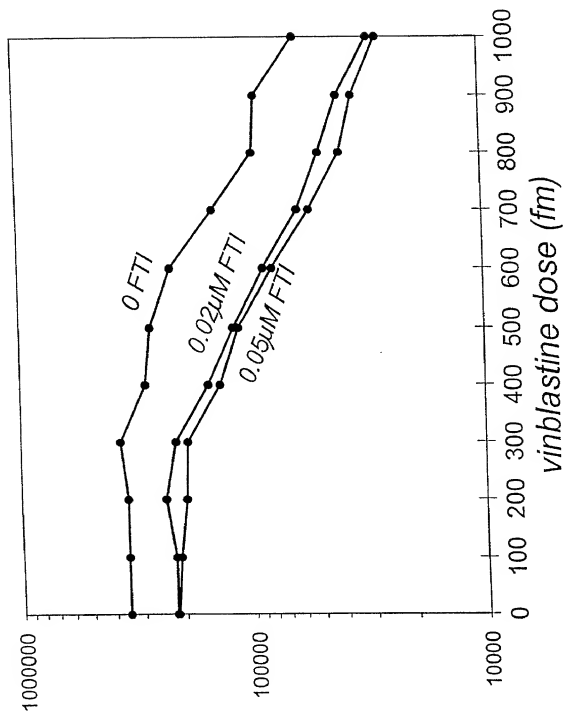


Fig. 17



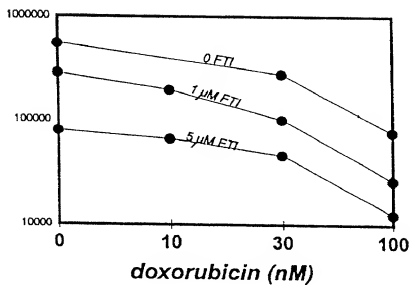


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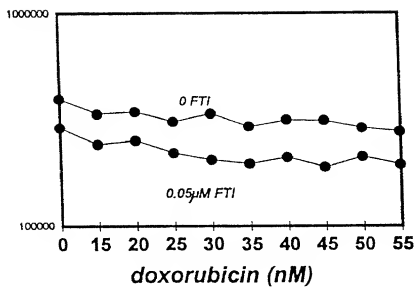


Fig. 19

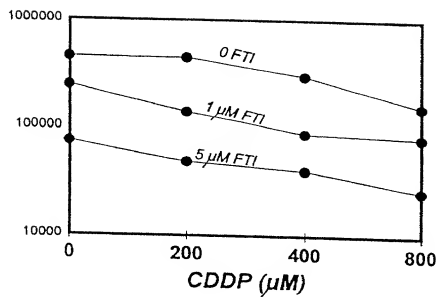


Fig. 20

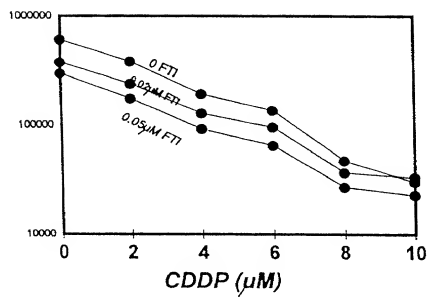


Fig. 21

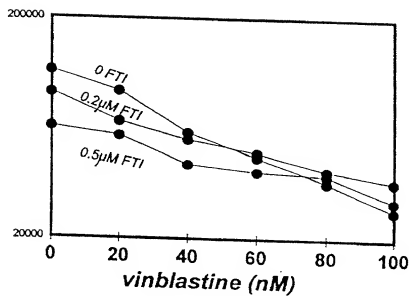


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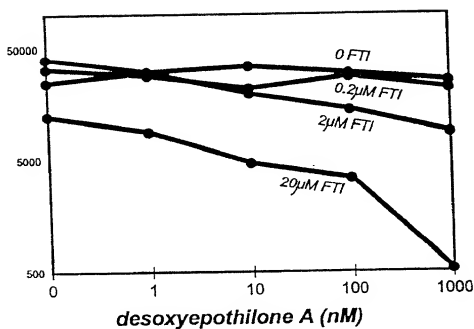
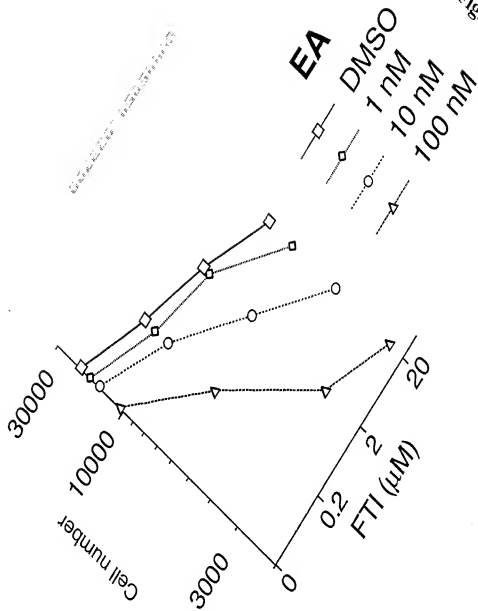


Fig. 23

Fig. 24



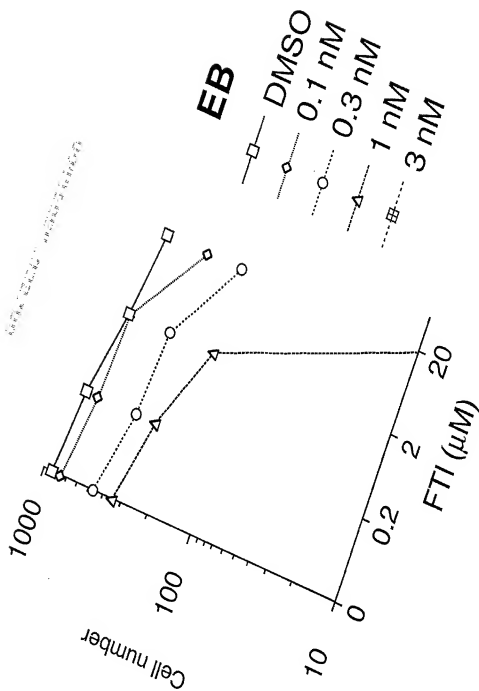
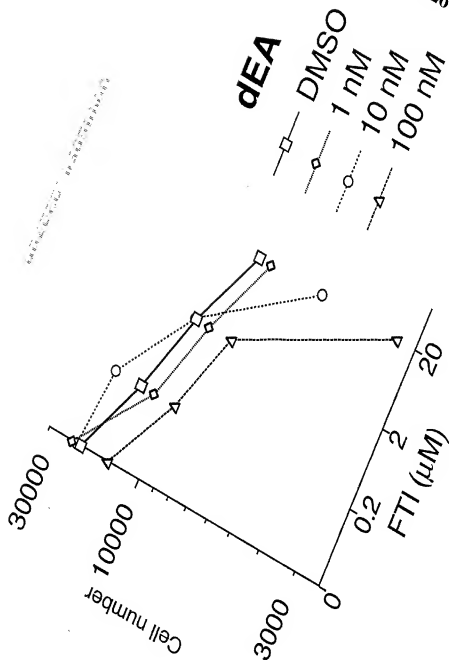


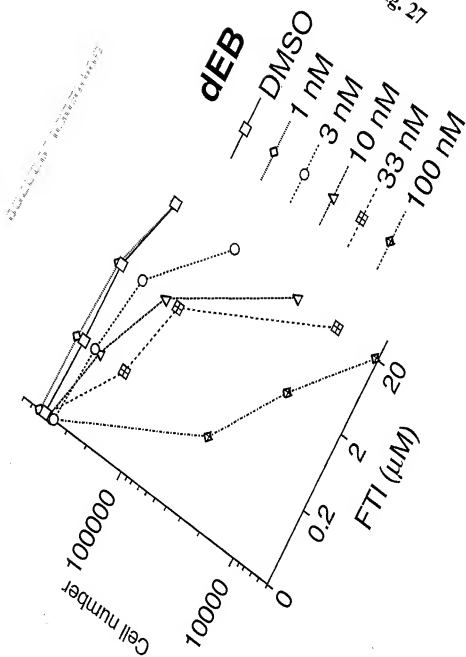
Fig. 25

Fig. 26



09/445054
PCT/US98/08646

Fig. 27



09/445054
PC105800046

Fig. 28

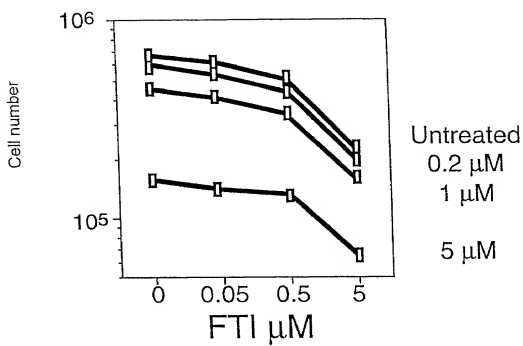


Fig. 29

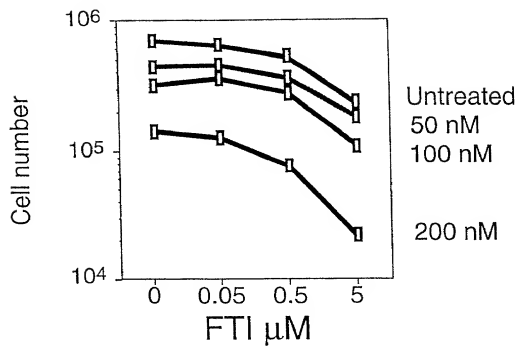


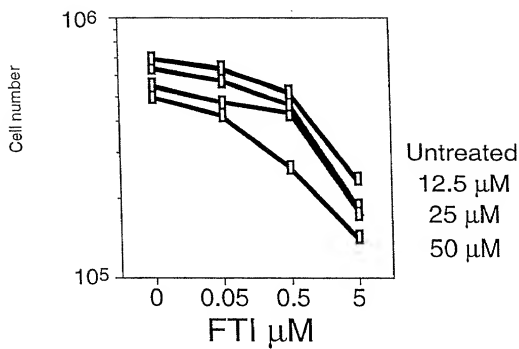
Fig. 30

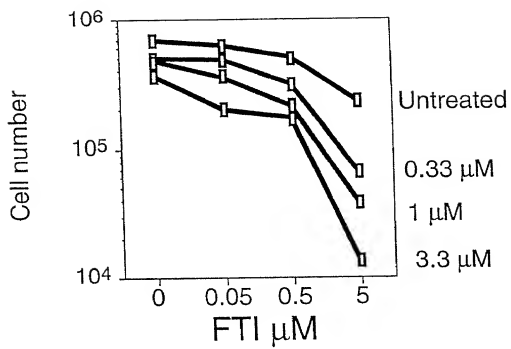
Fig. 31

Fig. 32

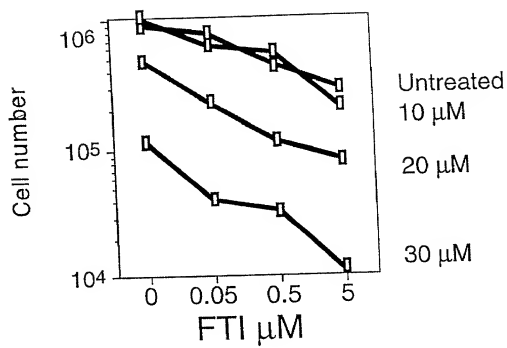
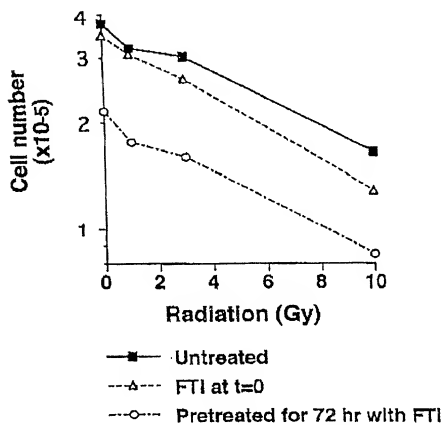


Fig. 33



COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY

(Includes Reference to PCT International Applications)

ATTORNEY'S DOCKET NUMBER

19962YP

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

A METHOD OF TREATING CANCER

the specification of which (check only one item below):

- ☐ is attached hereto.
- ☐ was filed as United States application

Serial No _____

on _____

and was amended

on _____

(if applicable).

- ☒ was filed as PCT international application

Number PCT/US98/08646on 4-Jun-1998

and was amended under PCT Article 19

on _____

(if applicable).

- ☐ is being filed as PCT international application, Attorney Docket No. _____

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

COUNTRY (if PCT, indicate "PCT")	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 USC 119
			<input type="checkbox"/> YES <input type="checkbox"/> NO
			<input type="checkbox"/> YES <input type="checkbox"/> NO
			<input type="checkbox"/> YES <input type="checkbox"/> NO
			<input type="checkbox"/> YES <input type="checkbox"/> NO
			<input type="checkbox"/> YES <input type="checkbox"/> NO

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (Continued) (Includes Reference to PCT International Applications)	ATTORNEY'S DOCKET NUMBER 19962YP
---	-------------------------------------

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, § 1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:

U.S. APPLICATIONS		STATUS (Check one)			
U.S. APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED	
60/048,736	5-Jun-1997			X	
PCT APPLICATIONS DESIGNATING THE U.S.					
PCT APPLICATION NO.	PCT FILING DATE	U.S. SERIAL NUMBERS ASSIGNED (if any)	PATENTED	PENDING	ABANDONED

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. (List name and registration number)

David A. Muthard
Regis. No. 35,297

Mark R. Daniel
Regis. No. 31,913

2

Send Correspondence to:

DAVID A. MUTHARD

Merck & Co., Inc.

P.O. Box 2000, 126 East Lincoln Avenue

Rahway, New Jersey 07065

Direct Telephone Calls to:

(name and telephone number)

(732) 594-3903

201	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
		Rosen	Neal	
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
		Englewood	New Jersey NJ	US
	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY	
	126 E. Lincoln Avenue	Rahway	New Jersey 07065	
202	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
		Sepp-Lorenzino	Laura	
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
		New Haven	Connecticut CT	US
	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY	
	126 E. Lincoln Avenue	Rahway	New Jersey 07065	
203	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
		Moasser	Mark	M.
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
		New York	New York NY	US
	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY	
	126 E. Lincoln Avenue	Rahway	New Jersey 07065	

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF INVENTOR 201	SIGNATURE OF INVENTOR 202	SIGNATURE OF INVENTOR 203
<i>[Signature]</i>	<i>[Signature]</i>	<i>[Signature]</i>
DATE	DATE	DATE
3/2/2000	March 7, 2000	3/2/2000

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (Continued)
(Includes Reference to PCT International Applications)

ATTORNEY'S DOCKET NUMBER

19962YP

Continuation of Inventor Information

204	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY	
205	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY	
206	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY	
207	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY	
208	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY	
209	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY	

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF INVENTOR 204	SIGNATURE OF INVENTOR 205	SIGNATURE OF INVENTOR 206
DATE	DATE	DATE
SIGNATURE OF INVENTOR 207	SIGNATURE OF INVENTOR 208	SIGNATURE OF INVENTOR 209
DATE	DATE	DATE